

STUDIES ON α - SUBSTITUTED ACYL GLYCEROLS
SYNTHESIS AND PHYSICAL PROPERTIES

Margareta Herslöf



Lund 1985



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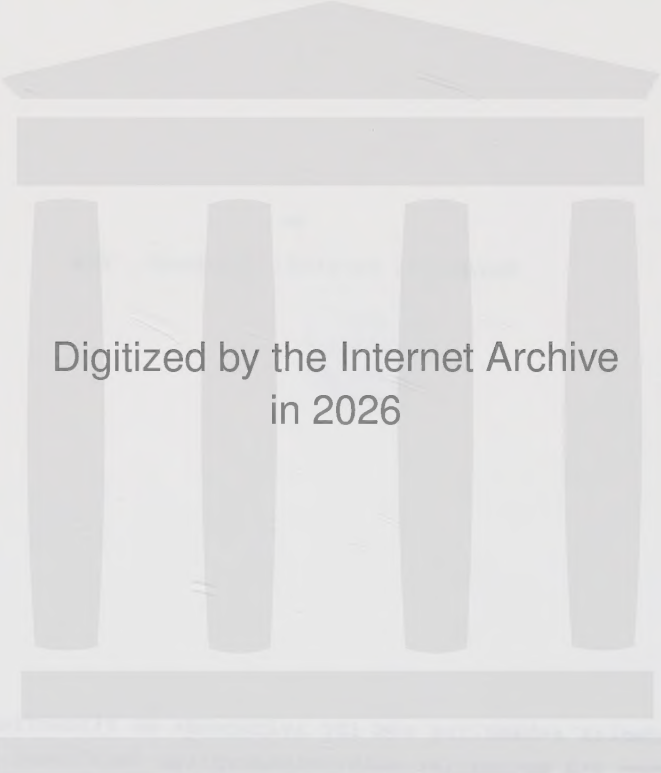
Synthesis and Physical Properties

av

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SYNTHESIS AND PHYSICAL PROPERTIES

Abstract The syntheses of the α -alkyl, α -phenylthio, α -phenylseleno, and α -carbomethoxy derivatives of monobutanoyl, monododecanoyl and monooctadecanoyl glycerol are described. The compounds were formed by reaction of the enolate anions of acylisopropylidene glycerols with electrophiles. Cleavage of the protecting group liberated the α -substituted monoacyl glycerols.

α -Alkylated monoacyl glycerols were also prepared by a multistep route via alkylation of fatty acid oxazolines. From the monoacyl glycerols the following α -substituted triacyl glycerols were obtained: 1- α -n-butylododecanoyl-2,3-didodecanoyl glycerol, 1,2-bis- α -n-butylododecanoyl-3-dodecanoyl glycerol, tris- α -n-butylododecanoyl glycerol, 1- α -phenylthiododecanoyl-2,3-didodecanoyl glycerol, 1- α -phenylselenododecanoyl-2,3-didodecanoyl glycerol and 1- α -carbomethoxydodecanoyl-2,3-didodecanoyl glycerol. α -Alkylation with triacyl glycerols as starting materials was performed via the tris-trimethylsilyl ketene acetals of tributanoyl glycerol and tridodecanoyl glycerol. Reaction of these acetals with t-butyl chloride and 1-adamantyl bromide in the presence of a Lewis acid gave mixtures of α -t-alkylated triacyl glycerols, as well as α -trimethylsilylated triacyl glycerols.

Rearrangements of the tris-trimethylsilyl ketene acetals to α -trimethylsilyl triacyl glycerols were carried out with zinc chloride in the absence of alkylating agents. The compounds prepared directly from straight chain triacyl glycerols were isolated by semi-preparative HPLC. Mass spectrometry and ^1H NMR spectroscopy of some of the derivatives are discussed.

Triacyl glycerols and triacyl glycerol mixtures were also prepared by interesterification. Polymorphism and flow behaviour of α -alkylated tridodecanoyl glycerols and of some interesterified triacyl glycerol mixtures are described. Compared to straight chain analogues, the introduction of α -branches lowered the phase transition temperatures. For tris- α -n-butylododecanoyl glycerol a glass transition at -70°C is proposed instead of a crystallization.

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Date 1985-09-19

This review gives a summary of the following papers, which will be referred to as I-VII.

- I. M. Herslöf, S. Gronowitz
Synthesis of 2-alkyl branched long-chain fatty acids and monoacyl glycerols.
Chemica Scripta 22, 230 (1983)
- II. M. Herslöf, S. Gronowitz
Enolate anions from lipid derivatives.
Alkylation of acylisopropylidene glycerols.
J. Am. Oil Chemists' Soc. 62, 1013 (1985)
- III. M. Herslöf, S. Gronowitz
Synthesis of 2-phenylthio-, 2-phenylseleno- and 2-carbomethoxy acyl isopropylidene glycerols.
Chemica Scripta, in press.
- IV. M. Herslöf, S. Gronowitz
Synthesis of trimethylsilyl ketene acetals from triacyl glycerols and their reaction with t-butyl chloride and 1-adamantyl bromide.
Chemica Scripta, accepted for publication.
- V. B. Herslöf, M. Herslöf, O. Podlaha
Simple small scale preparation of specific triglycerides and triglyceride mixtures.
Fette Seifen Anstrichmittel 82, 460 (1980)
- VI. L. Hernqvist, B. Herslöf, M. Herslöf
Polymorphism of interesterified triglycerides and triglyceride mixtures.
Fette Seifen Anstrichmittel 86, 393 (1984)
- VII. L. Bohlin, L. Hernqvist, M. Herslöf
Polymorphism and flow behaviour of some low melting α -alkyl branched triacyl glycerols.
Manuscript.

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1. INTRODUCTION

Vegetable oils are essentially composed of mixed triacyl glycerols with long chain saturated and unsaturated fatty acids. The naturally occurring fatty acids usually have an even number of carbon atoms between twelve and eighteen, and their double bonds are usually in the *cis* configuration. Vegetable oils differ in their fatty acid compositions and thus also in their triacyl glycerol compositions. As a consequence, the various oils have found uses in different areas. Most of them are consumed as edible products, although fats and oils have served as sources of fuels, soaps, lubricants and cosmetics for many centuries. Well known are for instance linseed oil, rich in linolenic acid, which is used as drying oil, and castor oil with a high content of ricinoleic acid, used in many industrial processes.

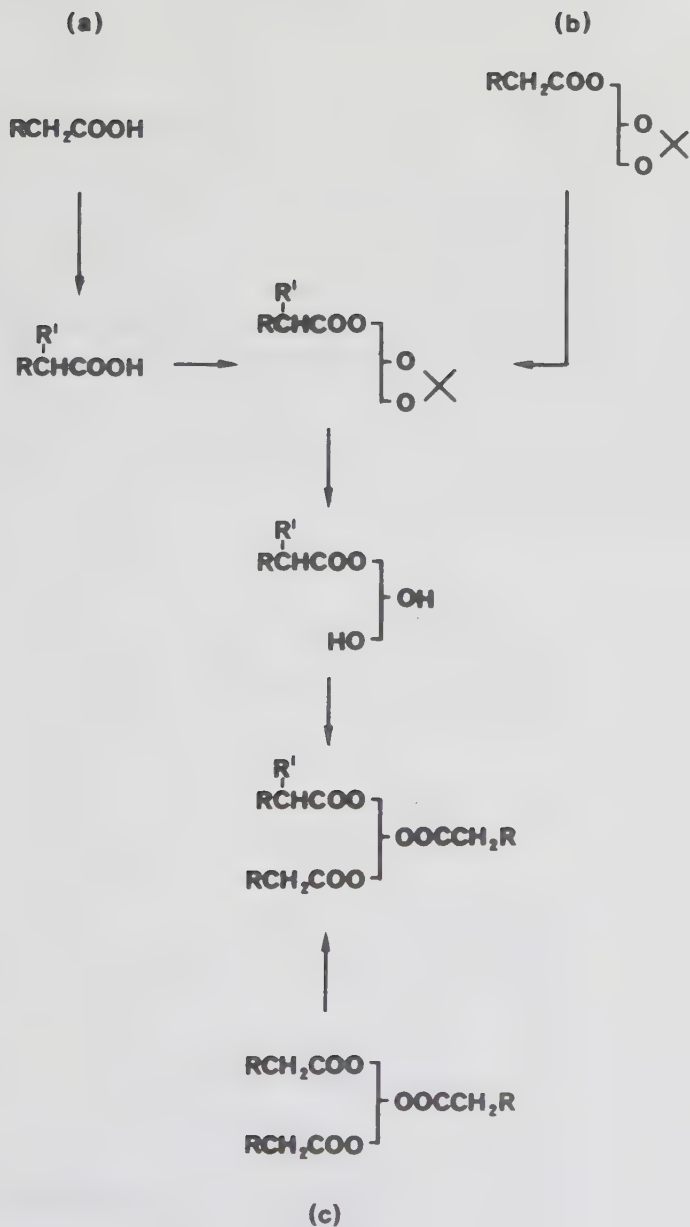
During the last few decades there has been a growing awareness of the significance of vegetable oils as renewable resources, with applications as fine chemicals, coatings, polymers and lubricants [1,2]. To increase the usefulness of fatty acids and vegetable oils, it should be beneficial to increase our knowledge about the synthetic chemistry of such systems. Research in synthetic lipid chemistry has been concentrated to the modification of fatty acids and simple fatty acid derivatives. This has been excellently reviewed [2,3].

In saturated fatty acids and esters, the α -position is the most reactive site in the hydrocarbon chain. Despite this, until recent years only few direct substitutions have had preparative value. Among these are halogenation [4] and sulfonation [5] in acidic media, and base-catalyzed Claisen condensation [6]. Free radical addition of acids to olefins [7-9] has been used to prepare α -alkylated fatty acids, although the alkylation of malonic esters [10] has been more frequently employed. Other indirect methods leading to α -substituted derivatives have involved formation through displacement of an α -halogen substituent [4]. The problems

with abstracting a proton from the slightly acidic α -methylene group were not solved until the development of strong non-nucleophilic bases in 1967 [11]. Since then, a number of papers that describe procedures to generate enolate anions from aliphatic acids and esters has been published [2,12,13]. The α -anions are versatile intermediates, since several derivatives are accessible by reaction with suitable electrophiles [2,13-30].

Little research has been performed on the preparation of α -substituted triacyl glycerols [31], especially on reactions starting from triacyl glycerols. The aim of this work has been to study the synthesis of α -substituted triacyl glycerols, with special interest in reactions usable with mono- and triglycerides as starting materials. The substituents, mainly alkyl groups, were chosen to give triacyl glycerols with new properties, like lower melting points and greater stability toward hydrolysis and oxidation. Lipid derivatives with such qualities might be interesting for future industrial use [32-37]. No vegetable oils containing α -alkyl branched triacyl glycerols are known, but such lipids have been identified in the preen glands of birds [38,39].

In principle it is possible to obtain α -substituted triacyl glycerols via three different approaches: a) In the first route the substituent is introduced into the fatty acid or its protected form. The triacyl glycerols can then be synthesized by esterification of glycerol or interesterification. b) In the second alternative the chemical modification is performed on the protected monoacyl glycerol and the triacyl glycerols are obtained after deprotection and subsequent acylation. c) Finally, it is also possible to make the α -substitution directly on the triacyl glycerol. This is an attractive possibility, since it might be extended to α -substitution of vegetable oils. The three alternatives are summarized in Scheme 1.



Scheme 1

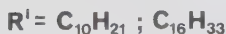
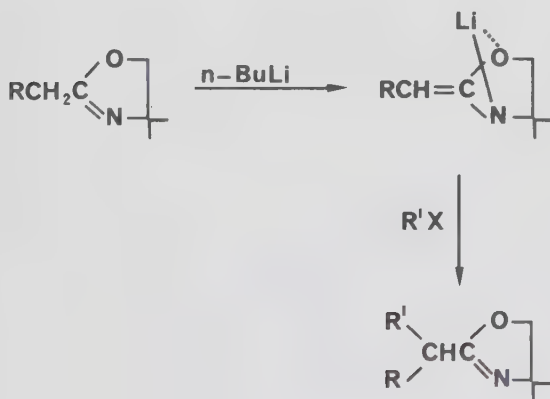
The preparation of branched fatty acids and their mono-glycerides (route a) is described in Section 2.1 (Paper I). The formation of triacyl glycerols through acylation and interesterification (Paper V) is reported in Sections 2.2.4 and 3 respectively. The polymorphic behaviour of the alkylated triacyl glycerols is discussed in Section 4 (Paper VII), as well as the polymorphic behaviour of some interesterified triglyceride mixtures (Paper VI). Reactions starting from protected monoacyl glycerols have also been studied, and the results are summarized in Section 2.2 (Papers II and III). In Section 2.3 results on the direct alkylation of some triacyl glycerols are collected (Paper IV).

2. SYNTHESIS OF α -SUBSTITUTED LIPID DERIVATIVES

2.1. Fatty acids as starting materials (Paper I)

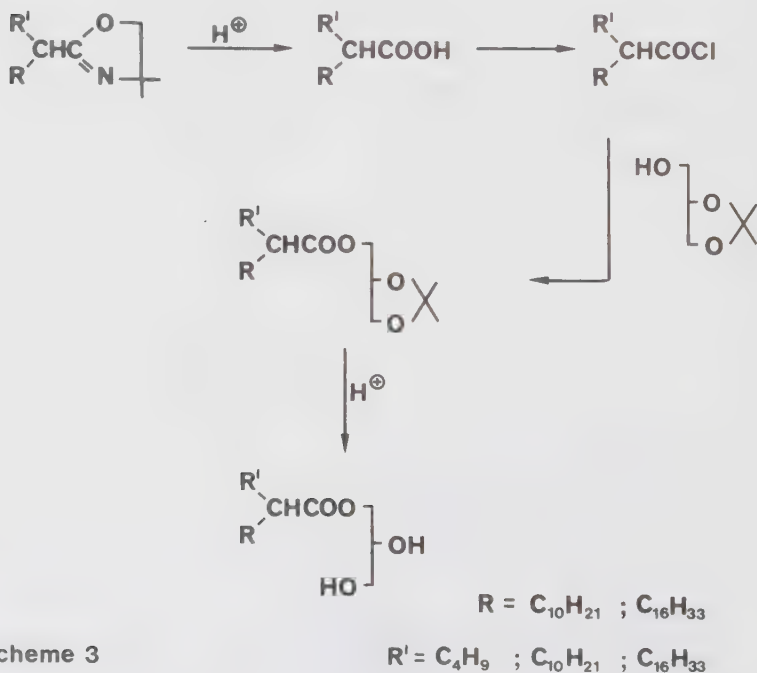
α -Alkyl substituted fatty acids have been prepared via alkylation of the corresponding 2-oxazolines, as described by Meyers [40,41].

The preparation of the 2-alkyl-4,5-dihydro-4,4-dimethyl-oxazoles was carried out either directly from the fatty acid and 2-amino-2-methyl-1-propanol, or stepwise from the acid chloride via the amido alcohol. The overall yield was 60-70% in both methods. The oxazolines from hexanoic, dodecanoic and octadecanoic acid were treated with *n*-butyllithium and alkyl iodides at -70°C , to give the α -alkyl branched oxazolines as shown in Scheme 2.



Scheme 2

Most of them were prepared in two ways: either a long chain oxazoline was alkylated with a short alkyl iodide, or a short chain oxazoline was alkylated with a long chain alkyl iodide. The α -alkylated oxazolines were isolated in yields ranging from 65-82%, irrespective of the route chosen. The branched oxazolines were hydrolyzed to the corresponding acids. Due to steric hindrance the α -alkyl oxazolines were more resistant to hydrolysis than the straight chain analogues. Prolonging the reaction time from 20 minutes to 3 days gave the α -alkyl fatty acids in yields varying from 60 to 85%. From the fatty acids the monoglycerides were prepared according to a standard procedure [42]. The reaction path is shown in Scheme 3. The overall yields of α -alkyl branched monoacyl glycerols starting from straight chain acids were 20-25%. The greatest advantage of the α -alkylation via the oxazolines compared to other alkylation methods [2] is the easy purification of the branched oxazolines by column chromatography.



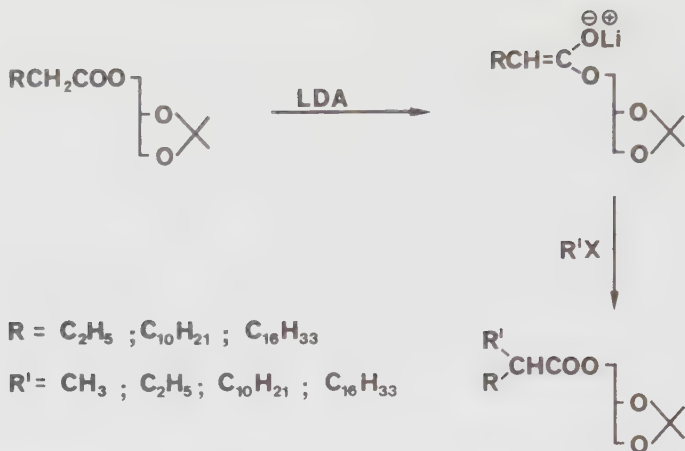
Scheme 3

2.2. Protected monoacyl glycerols as starting materials

Acylisopropylidene glycerols have been used as starting materials for the preparation of enolate anions. Butanoyl-, dodecanoyl- and octadecanoylisopropylidene glycerols were used as starting materials, in order to represent short, medium and long chain monoacyl glycerols. The anions of these compounds were reacted with alkyl halides [15,16] of different chain lengths (Paper II), disulfides [19-22] and diselenides [28-30] (Paper III). Carboxylation in the α -position was performed by reaction of the anions with carbon dioxide [24] or methyl chloroformate [23] (Paper III). The reactions are summarized in Schemes 4, 5 and 6.

2.2.1. Alkyl halides as electrophiles (Paper II)

The enolate anions of butanoyl- and dodecanoylisopropylidene glycerol were prepared at -70°C by the addition of lithium diisopropyl amide to the acylisopropylidene glycerols in THF. The solutions of the anions were transferred with cooling (-70°C) to solutions of the alkyl halides in THF-DMSO at room temperature. The yields of alkylated products after reaction with methyl, butyl, decyl and hexadecyl iodide were between 60 and 90%. With octadecanoylisopropylidene glycerol as starting material, no alkylated products were formed under identical conditions. This was probably due to the low solubility of octadecanoylisopropylidene glycerol in THF at -70°C . When the temperature for anion formation was raised to between -40 and -20°C , alkylated products were formed in 50-75% yields after treatment with alkyl iodides in THF-DMSO at room temperature. The reactions are shown in Scheme 4.

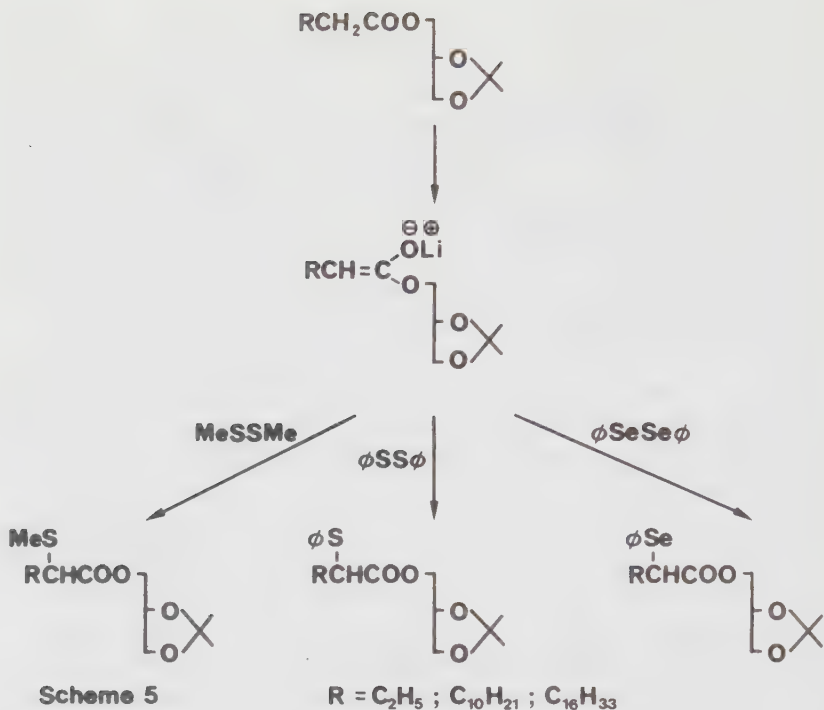


Scheme 4

The resulting alkylated acylisopropylidene glycerols were isolated by column chromatography or distillation. Acidic cleavage of the ketal group, as shown in Scheme 3, gave the α -alkyl branched monoacyl glycerols in an overall yield of about 35%, based on the straight chain free fatty acids. This may be compared with the 20-25% yields that were obtained when the α -alkylated monoacyl glycerols were prepared according to the multistep route via alkylation of oxazolines, as shown in Schemes 2 and 3. The reaction of the acylisopropylidene glycerols offers another advantage in that many different alkylated monoacyl glycerols can be obtained from the same starting material. It is also possible to introduce other groups into the molecules, here exemplified by the reaction with disulfides, diselenides and carboxylating agents (Paper III).

2.2.2. Disulfides and diselenides as electrophiles (Paper III)

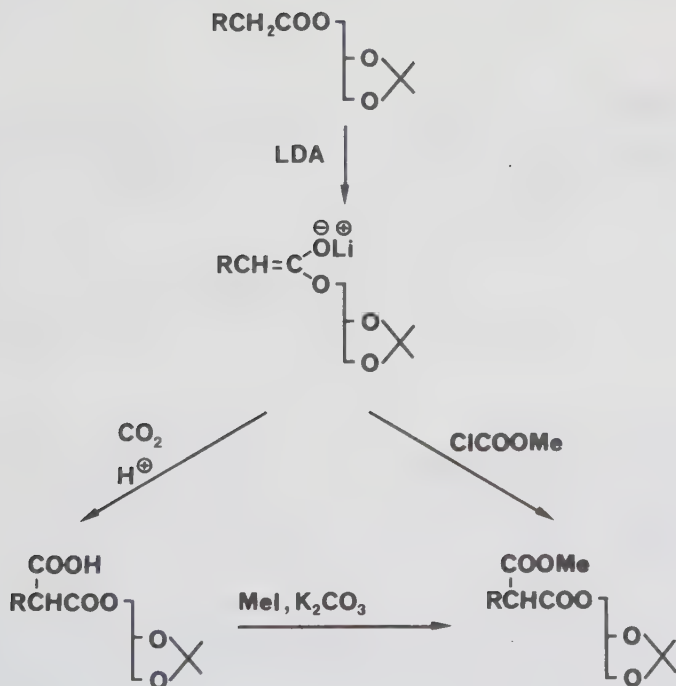
In the sulfenylation reactions of the enolate anions (Scheme 5) the product yields were influenced by the reactivity of the disulfide and by the chain length of the acylisopropylidene glycerol. With dimethyl disulfide as electrophile, about 50% of the α -methylthiobutanoylisopropylidene glycerol was formed according to GLC. With the anions of dodecanoyl- and octadecanoylisopropylidene glycerols, only between 20 and 30% of the α -methylthio substituted acylisopropylidene glycerols were obtained. Unlike the reactions with alkyl halides, some starting material was also found (15%). This might be formed by desulfenylation of the reaction product back to the starting acylisopropylidene glycerol, a reaction reported by Trost and Salzmann [43]. In the reaction of the enolate of butanoylisopropylidene glycerol with dimethyl disulfide, some of the side products are probably condensation products with or without thiomethyl groups. The more reactive diphenyl disulfide gave higher yields of the α -sulfenylated products. According to GLC, the yields were 68-69% after reaction with the three different acylisopropylidene glycerols. The isolated yields were between 40 and 50%, with the lowest yield for 2-phenylthiooctadecanoylisopropylidene glycerol. Reaction of the acylisopropylidene glycerols with diphenyl diselenide gave results similar to those in the reaction with diphenyl disulfide.



2.2.3. Carbon dioxide and methyl chloroformate as electrophiles (Paper III)

Polar groups were introduced into the acylisopropylidene glycerols by reaction of the enolate anions with carbon dioxide and methyl chloroformate. The resulting α -carboxyacetylisopropylidene glycerols were methylated with methyl iodide in acetone in the presence of potassium carbonate [44]. The yields of the crude α -carboxyacetylisopropylidene glycerols were between 62 and 85%, and the overall yields after the transformation to methyl esters were 40-55%. Higher yields (40-71%) were obtained by the reaction of the anions with methyl chloroformate, but the purification of these compounds was

more complicated than that of those with a free carboxyl group. The reactions are summarized in Scheme 6.

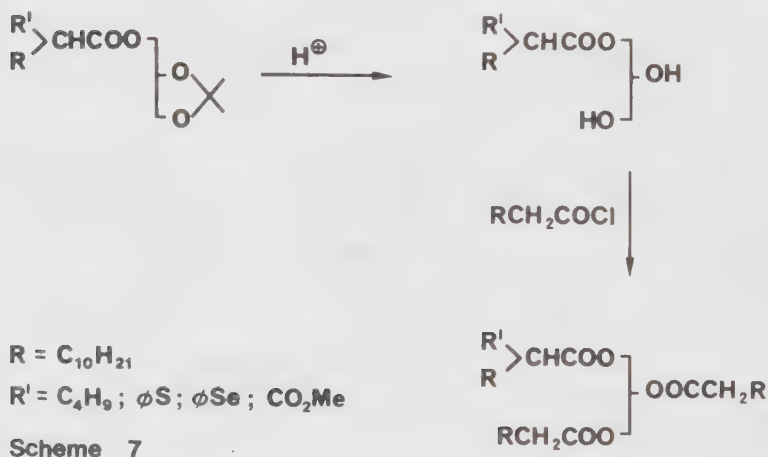


$\text{R} = \text{C}_2\text{H}_5; \text{C}_{10}\text{H}_{21}; \text{C}_{16}\text{H}_{33}$

Scheme 6

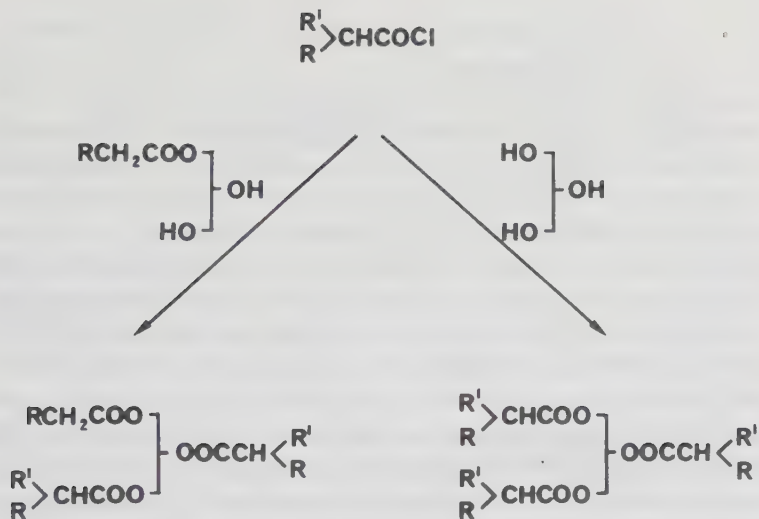
2.2.4. Synthesis of triacyl glycerols

From the α -substituted acylisopropylidene glycerols described in sections 2.2.1-2.2.3, the corresponding triacyl glycerols, of potential interest as lubricating agents, could be obtained. This was exemplified by the preparation of some triacyl glycerols from the α -substituted dodecanoyl derivatives. The reactions were performed according to standard procedures described in the literature [42], as summarized in Scheme 7.

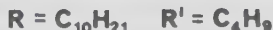


By the use of mono- α -butyldodecanoyl glycerol, the tri-dodecanoyl glycerol containing one butyl group was prepared. The tridodecanoyl glycerols with two and three butyl groups were obtained by reaction of monododecanoyl glycerol or glycerol with α -butyldodecanoyl chloride as shown in Scheme 8.

The triacyl glycerol containing three α -decyldodecanoyl groups was also prepared (Paper VII). The α -alkyltriacyl glycerols had lower melting points than the corresponding straight chain analogues, as expected. This is discussed in Section 4.



Scheme 8



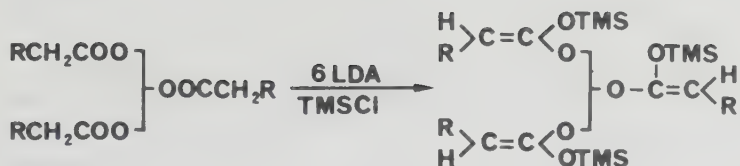
While the syntheses of the α -phenylthio- and α -phenyl-selenotridodecanoyl glycerols were straightforward, the preparation of the α -carbomethoxytridodecanoyl glycerol was more complicated. After acylation of the monoacyl glycerol with dodecanoyl chloride, three products were formed in the proportions 1.2:1.7:1.0 according to GLC. These compounds could not be separated by column chromatography on silica gel or by preparative TLC. HPLC-separation on a reversed phase column is currently being investigated. The compounds will be isolated by semi-preparative HPLC and the structures determined.

Mass spectra and ^1H NMR spectra of some of the triacyl glycerols prepared in this work are discussed in Section 2.4.

2.3. Triacyl glycerols as starting materials (Paper IV)

Application of the method described in Section 2.2 to the synthesis of triacyl glycerols was unsuccessful. Compared to simple alkyl esters, the triacyl glycerols are likely to have a greater tendency to undergo self condensation, since there are always possibilities for internal reactions. To circumvent these problems, it was desirable to trap the enolate anions by the use of a reactive electrophile, before condensation took place. The electrophile of choice was trimethylsilyl chloride (TMSCl), which is very reactive at low temperatures and is also compatible with lithium diisopropyl amide (LDA), and thus can be present when the anions are formed [45]. The O-trimethylsilyl ketene acetals formed by the reaction of ester enolates with TMSCl are rather stable compounds that can be handled at room temperature, as long as acids are avoided [25,26]. According to the literature, they are also versatile, since several derivatives can be obtained by further reactions without the use of strongly basic media. It is for instance possible to perform α -t-alkylations [46-48], α -acylations [49], aldol additions [50,51], Michael additions [52,53] and oxidations [54]. Alkenyl and alkyl groups can be introduced in the α -position through alkylation with the phenylsulfinyl chloride adduct of alkenes [55], or through alkylation with chloromethyl phenyl sulfide [56].

The trimethylsilyl ketene acetals of tributanoyl glycerol and tridodecanoyl glycerol were formed by the addition of the triacyl glycerols to cooled solutions of LDA and TMSCl in THF. By the use of two equivalents of LDA per acyl group silyl ketene acetals containing three trimethylsilyloxy groups were formed, as shown in Scheme 9.

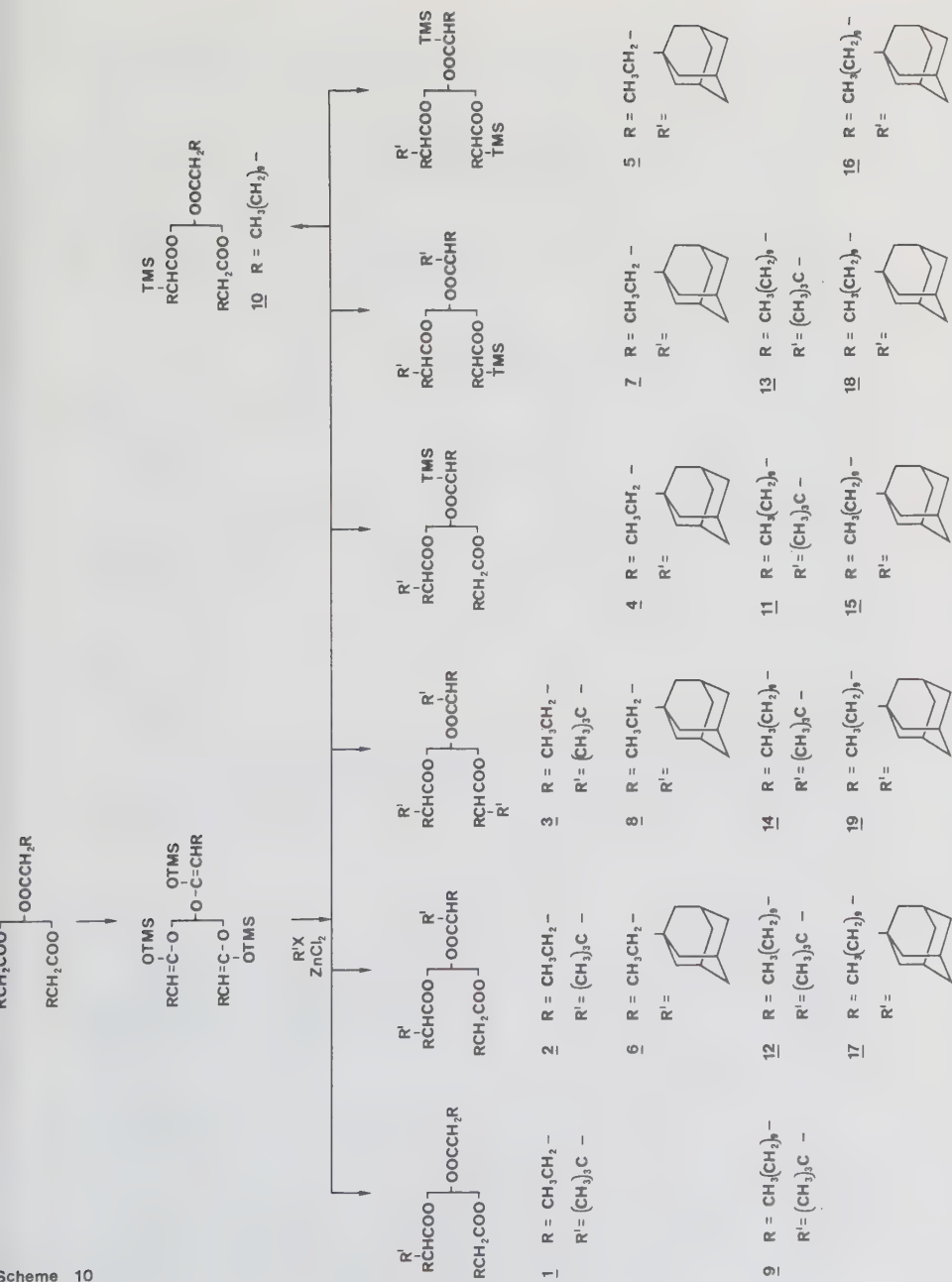


Scheme 9

With tridodecanoyl glycerol some unreacted starting material was also obtained. Analyses of the product mixtures by ^1H NMR spectroscopy indicated that no trimethylsilyl ketene acetals with only one or two trimethylsilyloxy groups were formed under the conditions used. The ^1H NMR spectra also showed that the E forms of the ketene acetals were probably obtained, since the vinyl protons appeared at $\delta = 3.64$ ppm [51,57,58]. This is the expected isomer when the reaction is kinetically controlled [45]. With three equivalents of base, the amounts of unreacted triacyl glycerols were increased, but mixed ketene acetal-acyl glycerols were still not formed. The addition of the cooled (-70°C) base to cooled (-70°C) mixtures of the triacyl glycerols and TMSCl also gave mainly ketene acetals containing three trimethylsilyloxy groups and starting material, probably together with some mixed ketene acetal-acyl glycerol. This behaviour suggests that the triacyl glycerols reacted in all three positions immediately when they were added to the LDA-TMSCl mixtures, and that some of the base was consumed in side reactions before the addition of the triacyl glycerols was completed, leaving some unreacted starting material. By adding the base to the triacyl glycerol and TMSCl the probability for the formation of ketene acetals with one and two TMS groups was increased, since the triacyl glycerol was present in excess during the reaction. Hydrolysis of the trimethylsilyl ketene acetals regenerated the starting material, together with small amounts of C-silylated compounds.

The trimethylsilyl ketene acetals from tributanoyl glycerol and tridodecanoyl glycerol were reacted with *t*-butyl chloride and 1-adamantyl bromide in the presence of zinc chloride in methylene chloride, according to the method described by Reetz and his coworkers [46,47]. The reactions and the products formed are shown in Scheme 10. The reaction of the trimethylsilyl ketene acetal of tributanoyl glycerol with *t*-butyl chloride was studied in some detail. It was then found that three new compounds were always formed. They were identified by GLC-MS (CI) to be the tributanoyl glycerols containing one, two and three α -*t*-butyl groups (compounds 1-3 in Scheme 10). Some starting material was also obtained. These results were always obtained, even though the starting ketene acetal contained three trimethylsilyloxy groups according to ^1H NMR spectroscopy. The highest yields of α -alkylated products were obtained when the trimethylsilyl ketene acetal, formed by the addition of the tributanoyl glycerol to a cooled solution of TMSCl and LDA (2 equiv./acyl group), was reacted with *t*-butyl chloride (1 equiv./acyl group) and zinc chloride in methylene chloride at room temperature. The reaction was complete in one hour. From the crude mixtures thus obtained, the triacyl glycerol fraction was isolated in about 50% yield. The specific triacyl glycerols were isolated by repeated flash chromatography and were characterized by ^1H NMR spectroscopy, MS (CI) and elemental analyses. It should be noted (Scheme 10) that only the kinds and numbers of the substituents were determined, and not in which of the acyl chains (1, 2 or 3) the substituents actually were situated. The purified triacyl glycerols might thus be mixtures of several positional isomers. In addition, new asymmetric centra were created during the α -alkylation, generating mixtures of diastereomers.

The reaction conditions described above (except that the reaction time was two hours) were used to alkylate tributanoyl glycerol with 1-adamantyl bromide, leading to the formation of five new products (4-8 in Scheme 10). They were isolated in the form of a triglyceride fraction, and each triacyl glycerol was purified by semi-preparative HPLC and characterized by ^1H NMR spectroscopy, MS (CI) and elemental analyses.

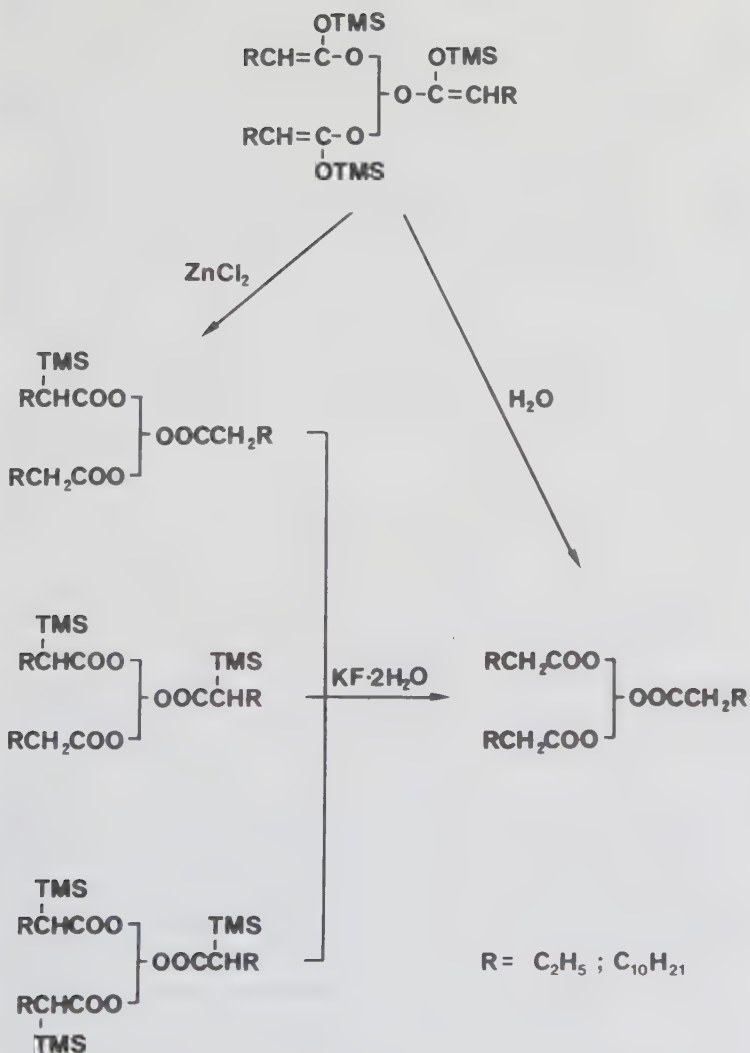


It was found that in addition to the α -adamantyltriacyl glycerols **6** and **8**, the triacyl glycerols containing both α -adamantyl and α -trimethylsilyl groups were formed. Products with alkyl groups and α -trimethylsilyl groups were also formed in the reactions of tridodecanoyl glycerol with *t*-butyl chloride and 1-adamantyl bromide (**10,11,13** and **15,16,18** in Scheme 10 respectively). All compounds were isolated and identified by ^1H NMR spectroscopy and MS (CI). The spectra will be discussed in Section 2.4. The yields of the triacyl glycerol fractions were between 40 and 80%.

The formation of the α -trimethylsilyltriacyl glycerols was quite unexpected. Since the hydrolysis of the silyl ketene acetals gave only minor amounts of C-silylated products, it seemed reasonable to believe that the α -TMS groups were introduced through a rearrangement during the alkylation. It was indeed found that treatment of the trimethylsilyl ketene acetal of tributanoyl glycerol with zinc chloride in methylene chloride at room temperature in the absence of alkylating agent, led to the formation (GLC-MS (CI)) of the α -trimethylsilylbutanoyl glycerols shown in Scheme 11. The α -TMS derivatives were beginning to form after 15 minutes, and after 2 hours the composition of the mixture did not change. This reaction thus appeared to be somewhat slower than the alkylation of the same ketene acetal with *t*-butyl chloride. This would explain why α -TMS derivatives are not found in the *t*-butylation of the tributanoyl glycerol.

Rearrangements to the α -TMS esters instead of alkylations have been reported only when the TMS ketene acetals of acetates were used as starting materials [46,59]. Others have reported that treatment of ketene acetals with Lewis acids in the absence of alkylating agents results in the formation of β -keto esters or/and succinate products [60-62].

Desilylation of the α -trimethylsilyltributanoyl glycerols with potassium fluoride regenerated the starting material (Scheme 11). When the crude *t*-butylated tributanoyl glycerol mixture was desilylated under identical conditions, the product composition did not change, further indicating that no α -silylated products were formed in this particular reaction.



Scheme 11

The reactions of the ketene acetals of tributanoyl glycerol and tridodecanoyl glycerol with adamantyl bromide, and of the ketene acetal of tridodecanoyl glycerol with t-butyl chloride, needed two hours for completion. The rate of formation of the α -silylated derivatives through rearrangement could thus be comparable. The α -trimethylsilylated compounds in the product mixtures could be desilylated leaving the compounds containing the t-butyl and adamantyl groups. In this way, the purification of the reacted triacyl glycerols was facilitated.

2.4. Mass spectrometry and ^1H NMR spectroscopy of the lipid derivatives

2.4.1. Mass spectrometry

The derivatives prepared in Sections 2.1 to 2.3 were characterized by electron impact or chemical ionization mass spectrometry. The compounds were satisfactorily identified, and only some of the fragmentation patterns will be discussed.

The EI-MS of the α -branched oxazolines described in Section 2.1 were easily interpreted. The most prominent fragments in the mass spectrum are those containing the oxazoline ring. The molecular ion M^+ is always present, as well as the $(\text{M}-1)^+$ ion. Fragmentation of the $(\text{M}-1)^+$ ion by loss of methylene groups gives rise to two different ions in the α -branched structure. McLafferty rearrangements of the molecular ion occur in two directions, giving two fragments as a result of the branched structure. These species undergo further fragmentation down to m/e 126, which is the base peak. It is thus possible to identify α -branched oxazolines by mass spectrometry. The fragments from the McLafferty rearrangements give information about the chain lengths of the branches, and the base peak at m/e 126 indicates an α -branched structure. The base peak in the straight chain analogue occurs at m/e 113. The fragmentation pattern of oxazolines is similar to that of pyrrolidines. [63,64].

Mass spectrometric analyses of fatty acids are usually performed on the methyl esters. Such analyses of α -branched fatty acid methyl esters have been reported [65,66]. Characteristic fragments were found due to cleavage at the α -position, resulting in loss of the carbomethoxy group, and McLafferty rearrangements. Ions that are characteristic of paraffins and olefinic compounds were also formed.

The electron impact mass spectra of the α -substituted acylisopropylidene glycerols, prepared in Section 2.2, gave fragmentations similar to those reported [66]. However, the α -phenylthio- and α -phenylselenoacylisopropylidene glycerols showed molecular ions. This was not observed in the unsubstituted acylisopropylidene glycerols, nor in the α -alkyl or α -carbomethoxy derivatives.

Analyses of straight chain triacyl glycerols with EI-MS usually gives very low intensities of the molecular ions [66,67], and thus gives little information about the molecular weight. This was found to also be true for the α -substituted triacyl glycerols prepared in Sections 2.2.4 and 2.3. Exceptions were the α -phenylthio- and α -phenylselenotriacyl glycerols, for which the intensities of the molecular ions were about 10 rel. %. Much simpler mass spectra were obtained by the use of chemical ionization mass spectrometry [68,69] with ammonia as reagent gas. The compounds shown in Scheme 10 were analysed with CI-MS, and a majority of them gave the $[M+NH_4]^+$ ion as the base peak. The exceptions were compounds 14,16-19. The molecular weight of compound 19 was too high to be measured by the instrument. Among the few other fragments formed were the $[M-RCOO]^+$ ions. In the triacyl glycerols containing three different acyl groups (4, 11 and 15), the dominant $[M-RCOO]^+$ fragments were those in which the α -TMS acyl residues were cleaved off.

2.4.2. 1H NMR spectroscopy

High resolution (300 MHz) 1H NMR spectra were recorded to identify the trimethylsilyl ketene acetals and the α -alkylated triacyl glycerols prepared in Sections 2.2.4 and 2.3. The protons in the ketene acetal portions and the acyl portions

of the molecules showed the expected chemical shifts and coupling constants. The protons in the glycerol part of the molecules exhibited more interesting patterns. It was found that the glycerol protons in the trimethylsilyl ketene acetal gave a simple spectrum, in which the glycerol methylene protons gave a doublet at $\delta = 3.89$ ppm. The middle glycerol proton gave a pentet at $\delta = 4.37$ ppm. The coupling constant was 5.1 Hz.

The glycerol protons in a symmetrical straight chain triacyl glycerol gave the expected AA'BB'X spectrum. In this spectrum the methylene protons showed a geminal coupling, with a coupling constant of 12 Hz, and two vicinal couplings with $J = 4.4$ Hz and $J = 6.0$ Hz. Thus, the two methylene signals were split into eight lines at $\delta = 4.1$ -4.4 ppm (Fig. 1a). The signal from the methine proton was split into three triplets centered at $\delta = 5.25$ ppm.

An identical spectrum was obtained from the glycerol part of tris- α -n-decyldodecanoyl glycerol. This was expected since the molecule is symmetrical.

The glycerol part of the α -n-butyl substituted tridodecanoyl glycerols prepared as described in Section 2.2.4 gave more complicated ^1H NMR spectra. The signal from the four methylene protons in 1- α -n-butyl dodecanoyl-2,3-didodecanoyl glycerol was split into 24 lines (Fig. 1b), while the methine proton gave three triplets. The vicinal coupling constants were 4.4 Hz and 6.0 Hz and the geminal coupling constants were all 12 Hz. The presence of two asymmetric centra gives four possible stereoisomers: two enantiomeric pairs, which are diastereomers. The diastereomers might have given two different overlapping glycerol spectra, one similar to the AA'BB'X spectrum described above, and one in which the five protons had different chemical shifts and gave an ABCDX spectrum. The coupling constant J_{AB} was equal to J_{CD} ; J_{AX} was equal to J_{CX} , and J_{BX} was equal to J_{DX} . The result would thus be one spectrum in which the AA'BB' protons gave 8 lines and was overlapped by one spectrum with 16 lines from the ABCD protons (Fig. 1b). The intensities of the two spectra were approximately the same, indicating that equal amounts of the diastereomers were formed.

Another interpretation of this spectrum would be that the glycerol spectrum was obtained from three different isomers, each containing an AA'BB'X spin system. Three possible isomers that could be present are the two diastereomers mentioned above, together with the triacyl glycerol with the α -butyl group located in the 2-position of the glycerol. This isomer might have been formed through migration of the α -branched acyl group during the synthesis, although such a migration should be slow due to steric hindrance. According to the literature [70], the glycerol part of 1,2-diacetyl-3-myristoyl-sn-glycerol gave a ^1H NMR spectrum similar to the ABCDX spectrum described above.

The 1,2-bis- α -n-butyl dodecanoyl-3-dodecanoyl glycerol contains three asymmetric centra, giving four possible enantiomeric pairs, which are diastereomers. Theoretically four different compounds could be present in the ^1H NMR spectrum, and at least two were observed, similar to the above described AA'BB'X and ABCDX spectra (Fig. 1c). Of course the spectrum could be interpreted as a combination of three overlapping AA'BB'X spectra, indicating that three isomers would be present.

The tris- α -n-butyl dodecanoyl glycerol contains four asymmetric centra leading to sixteen possible stereoisomers, some of which are identical. This results in only four enantiomeric pairs, which are diastereomers. The ^1H NMR spectrum of the glycerol protons showed one isomer if it was assumed that the spectrum was an ABCDX spectrum, and two isomers if an AA'BB'X spectrum was assumed (Fig. 1d).

Finally, in the triacyl glycerols prepared according to Section 2.3, the pure products might contain positional isomers as well as stereoisomers. No attempts to separate these isomers were made, and as a consequence the glycerol parts of their ^1H NMR spectra were very complicated. No interpretation was made.

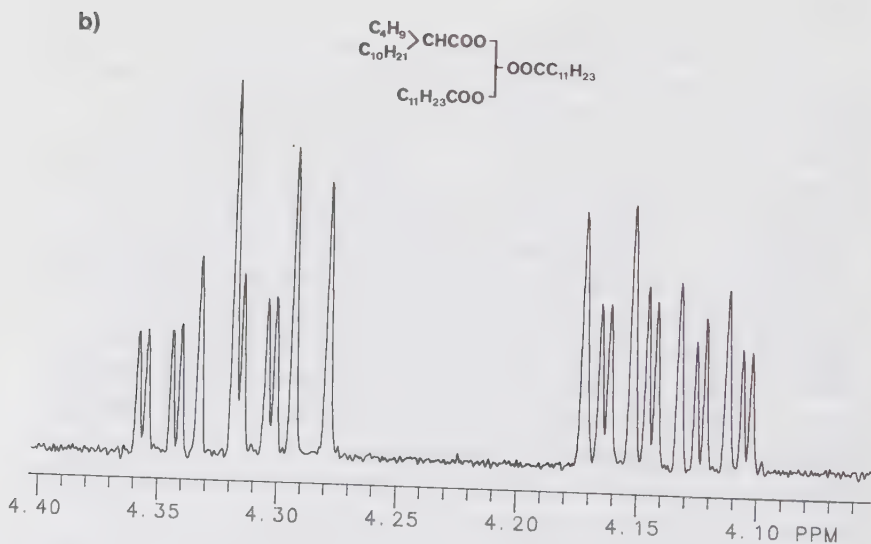
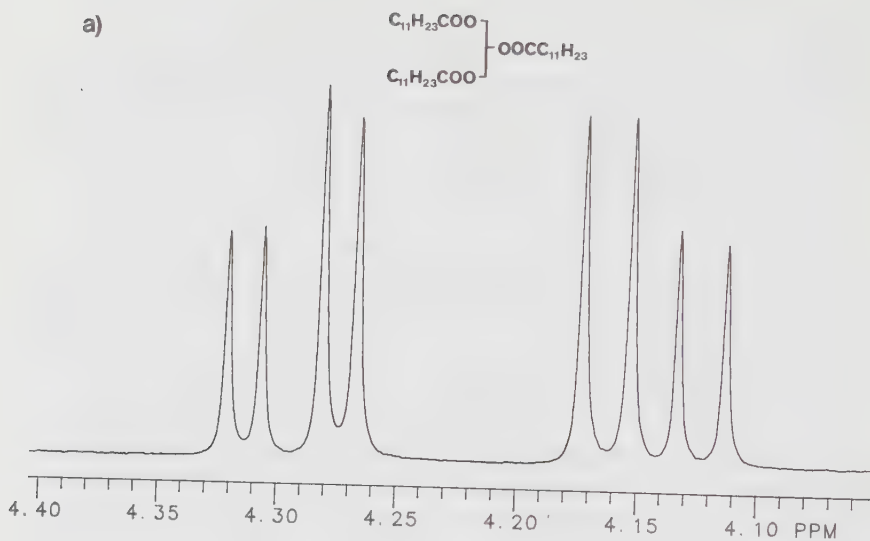
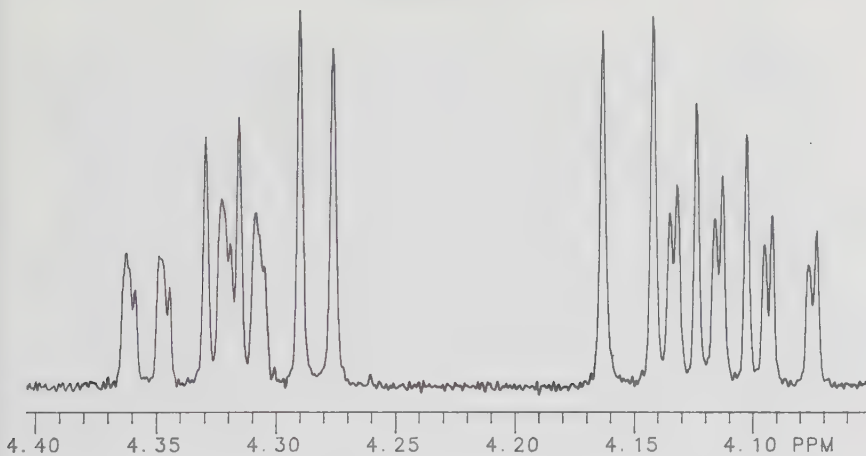
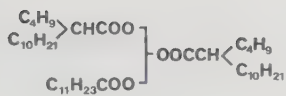
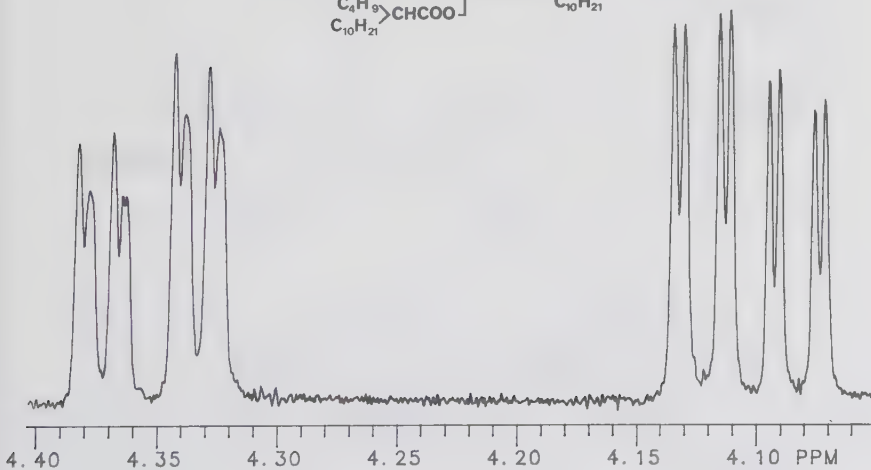
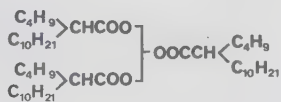


Figure 1. ^1H NMR spectra of the glycerol methylene protons in various triacylglycerols.

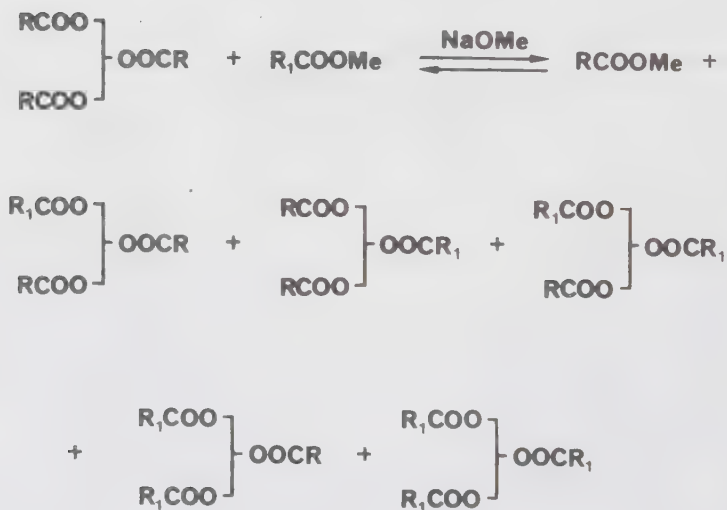
c)



d)



The preparation of specific triacyl glycerols and triacyl glycerol mixtures can be accomplished through interesterification. The ester interchange reaction is a very well studied reaction that offers a simple way to change the distribution of the fatty acid residues in triacyl glycerols [71-73]. By the influence of a catalyst, usually an alkali methoxide, the acyl groups are distributed in the new triacyl glycerols in a random manner (Scheme 12). Directed interesterifications may be obtained for instance by crystallization of one high melting component, resulting in a displacement of the equilibrium.



Scheme 12

In order to prepare the α -n-butyl substituted tridodecanoyl glycerols, the randomized interesterification reaction was used. Methyl α -n-butyl dodecanoate was interesterified with tridodecanoyl glycerol under nitrogen at 100°C. It was found from GLC and HPLC that the reaction was slow, and after 40 hours the expected statistical distribution was still not obtained (see Table 1). The slow reaction was probably due to the lowered reactivity of the more sterically hindered α -branched ester compared to the straight chain analogues. The long reaction time (40 hours) might also have had a negative effect on the catalyst, since the results were difficult to reproduce. Identical reaction conditions, but with four hours reaction time, were used in the interesterification of trilaurin with methyl heptadecenoate and with methyl palmitate, respectively (Paper V). In these cases, the equilibrium mixtures were easy to obtain, and the product mixtures contained the triacyl glycerols in the expected amounts, according to GLC and HPLC. The results are collected in Table 1. The triacyl glycerols containing heptadecenoic acid residues were isolated by semi-preparative HPLC.

Interesterifications were also carried out with mixtures of tristearin and triolein, and mixtures of tristearin and trielaidin, as described in Paper VI. The reaction products were analysed by HPLC and the distributions were found to be in accordance with those calculated for a completely random reaction. The polymorphic behaviour of the interesterified mixtures is described in Section 4.

Table 1. Distribution of the products from the
interesterification reaction

A Tridodecanoyl glycerol/methyl heptadecenoate 2:1(mol.equiv.)

	Calculated distribution		Experimental found values (area%)	
	(mol%)	(weight%)	GLC	HPLC
LaLaLa	63.0	60.2	60.3	60.7
LaLaH	31.5	33.3	33.5	33.7
LaHH	5.3	6.2	5.9	5.2
HHH	0.3	0.4	0.3	0.4

B Tridodecanoyl glycerol/methyl hexadecanoate 1:2

	Calculated distribution		Experimental found values (area%)	
	(mol%)	(weight%)	GLC	HPLC
LaLaLa	21.6	19.5	21.8	20.6
LaLaP	43.2	42.5	43.0	44.0
LaPP	28.8	30.6	29.1	29.1
PPP	6.4	7.3	6.2	6.3

C Tridodecanoyl glycerol/methyl α -n-butyldodecanoate 1:2

	Calculated distribution		Experimental found values (area%)	
	(mol%)	(weight%)	GLC	HPLC
LaLaLa	21.6	19.5	41.7	41.9
LaLaBuLa	43.2	42.5	44.0	47.0
LaBuLaBuLa	28.8	30.6	13.2	11.1
BuLaBuLaBuLa	6.4	7.3	1.1	0

La = dodecanoic, P = hexadecanoic, BuLa = α -n-butyldodecanoic,
H = heptadecenoic

4. POLYMORPHISM AND FLOW BEHAVIOUR OF SOME TRIACYL GLYCEROLS AND TRIACYL GLYCEROL MIXTURES

4.1. Background [74]

Triacyl glycerols in the solid state can be packed in various ways, and each crystal form can have its own melting point. This is called polymorphism, and has been well studied [74] with for instance X-ray diffraction and differential scanning calorimetry (DSC).

Triacyl glycerol molecules orient in different ways in the different crystal forms. In principle, two acyl chains in the molecules are arranged adjacently and the third points in the opposite direction. The hydrocarbon chains in the molecules can then be close-packed in different ways within this arrangement. In the liquid form the molecules are oriented roughly in the same way. The difference is the long range disorder and the high molecular mobility in the liquid state. The molecules normally form a double chain layer, but triple chain layers might occur when one chain differs much in length or is unsaturated. The crystal forms have different degrees of disorder in the hydrocarbon chains, giving each form a certain stability and melting point.

The crystal form with the highest disorder in the hydrocarbon chain is the α -form. In this form, the chains are packed according to a hexagonal subcell, with an oscillatory mobility of the acyl chains, and as a consequence the crystals in this form show the lowest melting point. This is the form usually obtained when a triacyl glycerol melt crystallizes. The methyl end group region of the molecules in the α -form is somewhat disordered. The α -form is not very stable and quickly transforms into the β' -form.

In this crystal form the hydrocarbon chains are arranged according to the orthorhombic subcell. The chains are more closely packed and do not show the same disorder as the α -form. Furthermore every hydrocarbon chain is perpendicular to its

neighbours. The methyl end groups are also packed in a better way in the double layer. This crystal form shows higher stability, and thus the molecules have higher melting points.

The most stable of the triacyl glycerol crystal forms is the β -form, in which the hydrocarbon chains are arranged according to the triclinic subcell. In this arrangement, all of the chains are parallel, which gives the best close packing of the triacyl glycerols. The β -form therefore has the highest melting point. In this form, the methyl end groups normally form a regular plane.

The three different crystal forms of simple triacyl glycerols, α , β' and β , are thus closely related to each other. The main difference is the way the dimers are arranged in relation to each other, and the way the hydrocarbon chains are close-packed. The different forms are shown schematically in Figure 2.

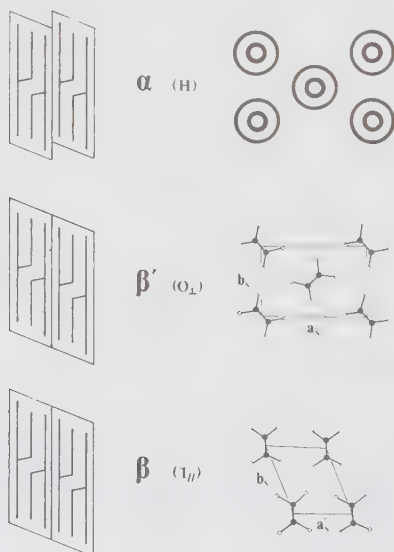


Figure 2. Schematic orientation of the triglyceride dimers of the α -, β' - and β -forms showed together with respective chain packing subcell. From Ref. [74]. Reprinted with permission of the author.

4.2. Polymorphic and rheological studies

The polymorphic behaviour of the interesterified tristearin/triolein and tristearin/trielaiddin mixtures obtained as described in Section 3 has been studied (Paper VI). The interesterified mixtures were prepared to contain triacyl glycerols with both saturated and cis or trans unsaturated acyl groups. The studies of these triacyl glycerols showed that while the presence of a cis double bond disturbed the formation of a double layer, the trans unsaturation only gave small distortions in the crystal packing. The melting points of the trans unsaturated triacyl glycerols were thus lower than those of the saturated analogues. The interesterified mixture of tristearin and triolein gave a triple chain structure in the sub- α - and α -forms, which disappeared when the $\alpha \rightarrow \beta$ ' transition occurred. By comparison with different blends of synthetic oleo-tristearoyl glycerols, it was proposed that the presence of rac-1-stearoyl-dioleoyl glycerol and 2-stearoyl-dioleoyl glycerol in the interesterified mixture was responsible for the formation of the triple chain layer. The disappearance of the triple layer at the $\alpha \rightarrow \beta$ ' transition coincided with the melting points of 2-stearoyl-dioleoyl glycerol and 1-stearoyl-dioleoyl glycerol. The crystallization process was dominated by the presence of tristearoyl glycerol, 2-oleoyl-distearoyl glycerol and rac-1-oleoyl-distearoyl glycerol.

The introduction of α -alkyl groups into saturated triacyl glycerols also influenced the polymorphic behaviour (Paper VII). Differential scanning calorimetry (DSC) and X-ray diffraction of 1- α -n-butyldodecanoyl-2,3-didodecanoyl glycerol, 1,2-bis- α -n-butyldodecanoyl-3-dodecanoyl glycerol and tris- α -n-decyldodecanoyl glycerol were studied. These compounds showed polymorphic behaviour similar to that of normal saturated triacyl glycerols. The main difference is that all transitions occurred at much lower temperatures. They crystallized in the α -form upon cooling, and with slow heating transitions to β '- and β -forms occurred in 1- α -n-butyldodecanoyl-2,3-didodecanoyl glycerol and tris- α -n-decyldodecanoyl glycerol before they melted at +19°C and +11°C, respectively. The 1,2-bis- α -n-

butyldodecanoyl-3-dodecanoyl glycerol melted directly from the α -form at -24°C .

The molecules were arranged in a bilayer in all of the polymorphic forms. The hydrocarbon chains were tilted toward the methyl end group plane, except in the α -form of tris- α -n-decyldodecanoyl glycerol. The tilting of the hydrocarbon chains increases the distance between the glycerol parts of two glycerol molecules. In this way, more room for the α -butyl chains is obtained without disturbing the close packing of the hydrocarbon chains. The third butyl group in tris- α -n-butyl-dodecanoyl glycerol seems to hinder the crystallization, and therefore a glass transition is proposed. It was not possible to study tris- α -n-butyldodecanoyl glycerol with DSC, due to instrumental limitations.

The flow behaviour, i.e. the steady shear rate viscosity and the oscillatory viscoelastic properties, of tris- α -n-butyldodecanoyl glycerol were measured using a Bohlin Rheometer system. The measurements were made at a constant shear rate, or at a constant frequency at small shear strains, as a function of the temperature down to -71°C . The oscillatory viscoelastic measurements indicated that a glass transition probably occurred at -68°C instead of a crystallization. The elasticity of the compound slowly increased when the temperature decreased from -53°C down to -68°C . The viscosity of the compound was low and slowly increased at lower temperatures.

Viscosity measurements of 1,2-bis- α -n-butyldodecanoyl-3-dodecanoyl glycerol and tris- α -n-decyldodecanoyl glycerol confirmed the crystallizations proposed above. The viscosity was low down to about -30°C , where the crystallization occurred.

It is evident from this study that tris- α -n-butyldodecanoyl glycerol has unique physical properties. It should therefore be of interest to study the polymorphic and flow behaviour of other α -substituted triacyl glycerols as well. In the tris- α -adamantyltriacyl glycerols for instance, the adamantyl groups are expected to disturb the close packing of the hydrocarbon chains even more, and thus lower the transition temperatures further. Long chain triacyl glycerols with oxidative

stability, which are in the liquid state down to very low temperatures (-70°C) have a potential as lubricants useful in cold climates.

5. ACKNOWLEDGEMENTS

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Synthesis of 2-Alkyl Branched Long-Chain Fatty Acids and Monoacyl Glycerols

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Abstract

In connection with attempts to prepare new additives for metal-working fluids from renewable resources, the α -alkylation of oxazolines of long-chain fatty acids has been investigated in detail. Some monoglycerides of α -branched fatty acids have been prepared.

Introduction

There is at present great interest in research concerning the use of renewable resources as substitutes for mineral oil as starting material for products of technical importance. Lipids derived from vegetable oils constitute such resources, and we have been interested in preparing long-chain 2-alkyl branched fatty acids and their corresponding monoglycerides in order to investigate their properties as additives in metal-working fluids. A natural route is to react α -anions derived from fatty acid derivatives, which has been developed during the last ten to twenty years [cf. 1, 2, 32]. The generation of α -anions from acids and esters is however connected with some problems.

First, the acidity of the α -methylene group is relatively low, while the reactivity of the carbonyl carbon towards nucleophiles is high. This means that a strong non-nucleophilic base is needed to produce α -anions.

It was not until 1967 that a suitable method was developed, when Creger [3-5] used lithium diisopropyl amide as base in the metalation of isobutyric acid. Since then, a number of papers has been published which describe procedures for the generation of enolate anions from aliphatic acids and esters [2].

A second problem is the large tendency of ester enolates to take part in condensation reactions [10]. However, this side reaction can in many cases be suppressed by using low reaction temperatures (-78°C), together with strong base [6, 7]. The condensation reaction can also be avoided by protecting the carboxylic groups against nucleophilic attack with a hindering moiety in *t*-butyl esters [6]. Another way of protecting the carboxylic group was developed by Meyers and his co-workers [8, 9]. They have found that the oxazoline derivative of acids are excellent starting materials for anion production. However, this reaction has not been applied to long-chain fatty acid oxazolines. In this case it is possible to use the nucleophilic butyllithium as base. No self condensation occurs, since the oxazoline has low carboxylic reactivity. At the same time the enamine anion is more reactive than the enolate anion. When the reaction of the anion with the electrophile is completed, the protective group can be removed to produce either the acid or ester derivative.

The third problem with α -anion preparation concerns the reaction of free acids. Dianions of acids do not undergo self condensation, but instead these anions have low solubility.

This leads to low product yields in the most used solvent, tetrahydrofuran. However the solubility of the dianion can be enhanced by using hexamethyl phosphoramide (HMPA) as a cosolvent [11]. The disadvantage is the suspected carcinogenicity of HMPA [12].

In a recent publication, Linfield and co-workers [28] report the use of amides of fatty acids as starting material for anion production. No HMPA is needed, and the reaction can be carried out at room temperature in benzene or THF. The yield of alkylated product is excellent.

Results and discussion

Of the various ways to prepare 2-alkylbranched fatty acids we have chosen the path via alkylation of 2-oxazoline derivatives, as shown in Scheme 1. The synthesis of fatty acid 2-oxazolines can be accomplished either directly from the acid and 2-amino-2-methylpropanol [15, 33] or from the acid chloride and 2-amino-2-methylpropanol via the corresponding amidoalcohol [17-19]. The overall yield for the two ways is about the same (60-70%) but for long chain fatty acids (i.e., stearic acid) the synthesis via amido-alcohol seems to be the most convenient. The direct methods lead to the formation of by-products, which makes the purification more difficult. From the fatty acid oxazoline we prepared the corresponding anion at -70° in THF using butyllithium as base. Reaction with alkyl halide gave the α -branched oxazoline derivative, which through treatment with aqueous acid gave the α -branched fatty acid [17]. Acylation of 1,2-isopropylidene glycerol with 2-alkyl-fatty acid chlorides followed by cleavage of the blocking group gave the mono-acylglycerols (Scheme 1) [13, 14].

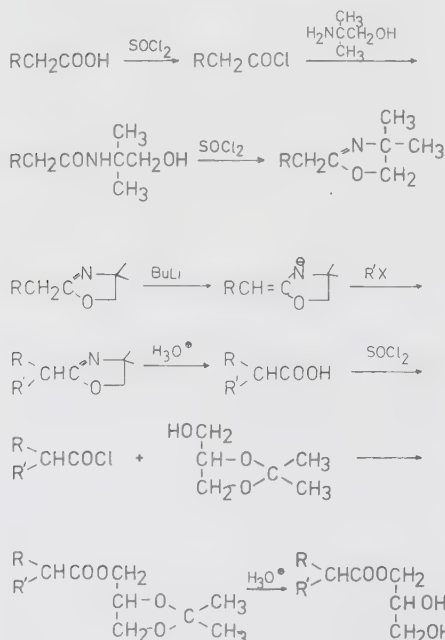
The preparation of oxazoline anions and their alkylation has some advantages over reactions that used fatty esters as starting materials for anion production and alkylation. Compared to the alkylation of ester enolates, the path via 2-oxazoline derivatives gives about the same over all yield (60%), but the purification of the product is much easier in the latter case. Separation of 2-alkylbranched fatty esters from starting material and ester condensation products can be achieved through distillation, but in particular for long chain or unsaturated compounds, this can be laborious. On the other hand the alkyl branched oxazoline can easily be separated from the starting material with ordinary column chromatography on silica gel. The straight chain oxazoline derivative stays on the column, probably due to hydrolysis on the slightly acidic column, while the branched product is eluted. Another advantage is that we do not need to prepare lithium diisopropylamide, but can use the commercially available butyllithium. The main disadvantage of the method is that the oxazoline derivative of the fatty acid has to be prepared in a separate step.

In most cases the preparation of the 2-alkyl fatty acid oxazoline can be made in two ways. We have found that even though the solubility of oxazolines and their anions is higher for shorter alkyl chains, this has no marked effect on the reaction time and yield of product. This means for instance that the reaction with hexanoic acid oxazoline and octadecanoic acid oxazoline with hexadecyl bromide and butyl bromide, respectively, gives almost the same GLC-yield of butyloctadecanoic acid oxazoline. Furthermore, the change of chain length in the alkyl halide does not change the yield of product. Thus, alkylation of dodecanoic acid oxazoline with butylbromide or hexadecyl bromide gave the same GLC-yield of alkylated product.

It was also possible to use either alkyl bromide or alkyl iodide without changing the result of the reaction.

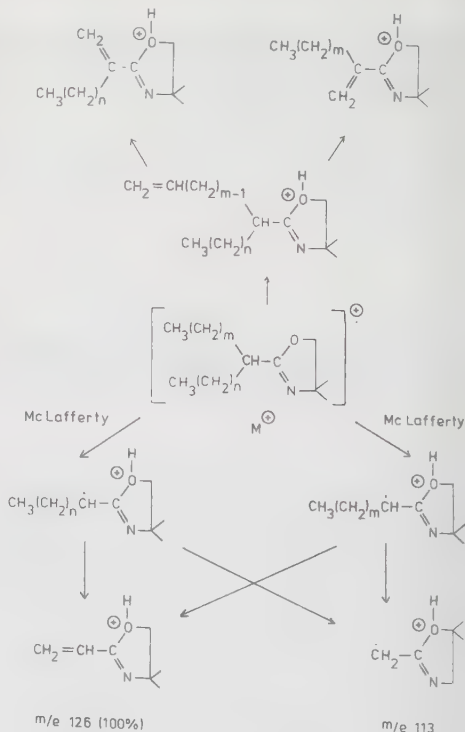
The reaction of the α -branched oxazolines towards hydrolysis is slower than that of the straight chain analogues, probably due to steric hindrance. According to Meyers [9], the hydrolysis can be carried out through reflux with hydrochloric acid for 15–20 min. For the branched oxazolines, these conditions lead to a mixture of fatty acid and the ring opened ester amine. Extension of the reaction time to 3 days gives complete hydrolysis to the fatty acid. As mentioned above, this difference in reactivity was utilized in the purification of the alkylated oxazolines. Once the branched fatty acid is formed, the synthesis of monoglyceride is straightforward, as shown in Scheme 1.

The mass fragmentation of oxazolines has been studied in some detail. As for pyrrolidides [29, 30], the fragmentation pattern is quite simple, and the most prominent peaks are due



Scheme 1

~ 25%



Scheme 2

to ions containing nitrogen, that is containing an oxazoline ring. A general fragmentation pattern is shown in Scheme 2.

The molecular ion M is always accompanied by an $M-1$ ion, with about the same intensity as the M ion. This $M-1$ ion then decomposes through loss of m/e 14 down to the fragments indicated in the scheme. The α -branched structures give rise to two different fragments through this path, while the straight chain analogues give the peak at m/e 126. McLafferty rearrangement of the molecular ion gives two different fragments as a result of the branched structure. Further fragmentation of the rearranged structure leads to the base peak at m/e 126.

For straight chain fatty acid oxazolines, the base peak appears at m/e 113. It is thus possible to identify α -branched oxazolines through the base peak at m/e 126 and to determine the chain lengths of the branches through the McLafferty fragments.

The 2-alkyl fatty acids and monoglycerides prepared in this work were tested in emulsifier system as emulsions used as lubricants in metal work. The results so far indicate that this system has a better bacteriostatic effect than the straight chain system. The largest effect was noted when branched fatty acids with carbon number 22 and 36 were used. However, the effect seems to be too small to motivate a replacement of straight chain emulsifier systems by branched chain systems.

Experimental

Melting points are uncorrected.

Solvents were dried by passage through a column with alumina, basic or neutral (Merck) or through reflux and distillation from sodium. ¹H NMR spectra were recorded on a Jeol MH-100 spectrometer.

Mass spectra were recorded at 70 eV on a LKB 9000 mass spectrometer or a Finnigan model 4021 mass spectrometer.

The gas chromatograph used was a Varian 1400 equipped with a flame ionization detector. The columns used were a 2 m x 1/8" SP2330 (10% on chromosorb WAW, 100/120 mesh) and a 0.5 m x 1/8" OV1 (1.5% on Gaschrom Q, 100/120 mesh), both glass columns.

Elementary analyses were performed by the Analytical department of the Chemical Center, University of Lund.

*Preparation of straight chain oxazolines from fatty acids**General methods [15, 17–19]*

Method A. Fatty acid (1 mol) and 1.3 mol of 2-amino-2-methyl-1-propanol were dissolved in 100 ml of xylene. The reaction mixture was refluxed with water separation at an oil bath temperature of 180–190°C. After about 20 h the reaction mixture was cooled and the xylene was distilled. The residue was chromatographed on neutral alumina (Merck) and eluted with ether. The evaporated product was distilled; yield 60–80%. The purity was checked by GLC, ¹H NMR and mass spectrometry. All oxazoline products showed a characteristic IR peak at 1670 cm⁻¹.

Method B. Fatty acid chloride was prepared from the corresponding acid and thionyl chloride in 90–95% yield [13]. To an ice-cooled solution of 0.1 mol of 2-amino-2-methyl-1-propanol in 180 ml of methylene chloride, 0.05 mol of fatty acid chloride in 30 ml of methylene chloride was added slowly at 0°C with stirring. The reaction mixture was stirred for another hour at 0°C and then at room temperature over night. The mixture was then washed with water, dried with MgSO₄ and evaporated. The crude product of fatty acid amidoalcohol was dissolved in 200 ml anhydrous ether and 0.2 mol of thionyl chloride was added dropwise with stirring at 0°C. After stirring for 5 min at 0°C the ether solution was added slowly with stirring to 550 ml of 2 M sodium hydroxide solution at 0°C. The phases were separated and the aqueous layer was extracted with ether. The combined ether solutions were dried over potassium carbonate and evaporated. The product was distilled.

4,5-Dihydro-4,4-dimethyl-2-pentylloxazole (caproic acid oxazoline). **Method A:** From 59.8 g (0.51 mol) of hexanoic acid and 50.8 g (0.58 mol) of 2-amino-2-methylpropanol in 50 ml xylene 57.4 g (67%) of oxazoline was obtained; b.p. 90–92°C/25 mm Hg. Lit. value [33]: 78°C/20 mm Hg.

4,5-Dihydro-4,4-dimethyl-2-undecylloxazole (lauric acid oxazoline). **Method A:** Dodecanoic acid (20.9 g, 0.1 mol) and 9.8 g (0.11 mol) of 2-amino-2-methylpropanol in 10 ml of xylene gave 17.4 g (69%) of lauric acid oxazoline with b.p. 145°C/3 mm Hg.

Method B: From 32.2 g (0.36 mol) of 2-amino-2-methylpropanol in 650 ml of methylene chloride and 39.5 g (0.18 mol) dodecanoyl chloride in 100 ml of methylene chloride was obtained 48.6 g (100%) amidoalcohol. This product (46.0 g) was cyclized with 72.6 g (44 ml, 0.61 mol) of thionyl chloride to give 35.3 g of the title product (78% from lauroylchloride):

b.p. 145–146°C/3 mm Hg. Lit. value [33]: b.p. 93°C/0.02 mm Hg.

4,5-Dihydro-4,4-dimethyl-2-heptadecylloxazole (stearic acid oxazoline) was prepared according to method A from 142.3 g (0.5 mol) of dodecanoic acid and 50.0 g (0.56 mol) of 2-amino-2-methyl-1-propanol in 50 ml of xylene; yield: 101.1 g (60%), b.p. 138–143°C/0.01 mm Hg, mp 24.0–25.5°C. Lit. value [33]: b.p. 173°C/0.3 mm Hg.

Method B: From 54.5 g (0.18 mol) of stearoyl chloride (13) in 100 ml of methylene chloride and 32.2 g (0.36 mol) of 2-amino-2-methyl-1-propanol in 550 ml of methylene chloride, 61.1 g (95%) of the amidoalcohol was prepared. Cyclization of this compound with 72.6 g (0.61 mol) of thionyl chloride gave 39.3 g of the title product (65% from the acid chloride).

Alkylation of fatty acid oxazolines

General procedure according to [8, 9]. The synthesis was performed under nitrogen with dry glass equipment and anhydrous solvents. Liquids were added with syringes through septa.

The oxazoline (10 mmol) was dissolved in 25 ml of anhydrous THF (80–120 ml in the case of stearic acid oxazoline). The solution was cooled to –78°, whereby the oxazoline precipitated. *n*-Butyllithium (11 mmol) in hexane was added, and the reaction mixture was stirred at –78°C for 1 to 2 h. After that time a clear yellow solution was obtained (except for stearic acid oxazoline). The alkyl halide (12 mmol) dissolved in 6–40 ml (depending on chain length) of anhydrous THF was added dropwise at –78°C, whereby a precipitate was formed. The reaction mixture was stirred for another 1 to 2 h. After that time the temperature was allowed to reach room temperature over night. As the temperature was rising the solution became clear. The mixture was poured into saturated ammonium chloride solution and ether was added. The phases were separated and the aqueous layer was extracted with ether. The combined ether layers were washed with saturated sodium chloride, dried over MgSO₄ and evaporated. According to GLC the oxazolines were alkylated to about 80–90%. The crude product was chromatographed on silica (ether–hexane 1:9). The remaining alkyl halide was eluted first and then the branched oxazoline. The straight-chain oxazoline stayed on the column. The yield after chromatography, and in some cases distillation, varied from 65–82%.

All alkylated oxazolines were identified by IR, ¹H NMR and MS, and purity was checked with TLC and GLC. Yields and physical data for the synthesis of

2-(1-butylundecyl)-4,5-dihydro-4,4-dimethyloxazole,
2-(1-decylundecyl)-4,5-dihydro-4,4-dimethyloxazole,
2-(1-butyloctadecyl)-4,5-dihydro-4,4-dimethyloxazole,
2-(1-decylheptadecyl)-4,5-dihydro-4,4-dimethyloxazole,
4,5-dihydro-4,4-dimethyl-2-(1-hexadecylheptadecyl)-oxazoline

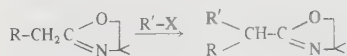
are summarized in Table I. Mass fragments are summarized in Table II.

General method for the hydrolysis of 2-alkyl substituted fatty acid oxazoline. Modified after Meyers [9]

The branched oxazoline (0.01 mol) was mixed with 10 ml of 6 M HCl. The mixture was refluxed for 3–7 days. After cooling the reaction mixture was worked up in two different ways.

A: The mixture was extracted with three portions of methyl-

Table I. Alkylation of oxazolines



R	R'·X	Yield %	Bp °C	Mp °C	Analyses	n_D^{20}
C ₁₀ H ₂₁	C ₄ H ₉ I	65	138–142 (0.2)	—	Calcd: C 77.61 H 12.70 N 4.52 Found: C 77.6 H 12.6 N 4.71	1.4484
C ₁₀ H ₂₁	C ₁₀ H ₂₁ Br	73	173–175 (0.02)	—	Calcd: C 79.32 H 13.06 N 3.56 Found: C 77.1 H 12.9 N 3.72	1.4538
C ₄ H ₉	C ₁₆ H ₃₃ Br	78	—	—	Calcd: C 79.32 H 13.06 N 3.56 Found: C 78.2 H 12.7 N 3.89	1.4540
C ₁₀ H ₂₁	C ₁₆ H ₃₃ Br	82	—	30.0–31.0	Calcd: C 80.43 H 13.29 N 2.93 Found: C 80.4 H 13.7 N 2.91	—
C ₁₆ H ₃₃	C ₁₆ H ₃₃ Br	82	—	45.0–46.0	Calcd: C 82.21 H 13.45 N 2.49 Found: C 81.1 H 13.8 N 2.50	—

Table II. MS-fragments of α -branched 2-alkyloxazolines

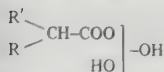
R	R'	m/e (rel %)							
C ₁₀ H ₂₁	C ₄ H ₉	308 (3)	308 (3)	294 (7)	266 (17)	182 (27)	253 (10)	169 (32)	126 (100)
C ₁₀ H ₂₁	C ₁₀ H ₂₁	393 (8)	392 (8)	378 (7)	266 (40)		253 (54)		126 (100)
C ₁₆ H ₃₃	C ₄ H ₉	393 (3)	392 (3)	378 (3)	350 (8)	182 (22)	337 (5)	169 (40)	126 (100)
C ₁₆ H ₃₃	C ₁₀ H ₂₁	477 (16)	476 (13)	462 (6)	350 (18)	266 (24)	337 (31)	253 (46)	126 (100)
C ₁₆ H ₃₃	C ₁₆ H ₃₃	(561) (1)	(560) (1)	(546) (1)	350 (30)		337 (20)		126 (100)

Table III. Physical data for 2-alkyl fatty acids: $\begin{array}{l} \text{R}' \\ \diagup \\ \text{R}-\text{CH}-\text{COOH} \end{array}$

R	R'	Yield %	Bp. °C (mm Hg)	Mp °C	Lit. value	Ref.
C ₁₀ H ₂₁	C ₄ H ₉	86	125–129 (10 ⁻⁴)	—	160–61 (0.4)	20
C ₁₀ H ₂₁	C ₁₀ H ₂₁	58	—	54.0–55.0	54–55	22
C ₄ H ₉	C ₁₆ H ₃₃	64	—	46.0–47.5	48–48.5	20
					45–46	23
C ₁₀ H ₂₁	C ₁₆ H ₃₃	60	—	61.0–63.0	58–59	24
C ₁₆ H ₃₃	C ₁₆ H ₃₃	80	—	76.5–78.0	73–74	24
					68–69	21

ene chloride. The combined organic phase was washed with methylene chloride and acidified with HCl under cooling and stirring. The acid was taken up in methylene chloride. The organic phase was dried over MgSO₄ and evaporated.

B: When the reaction mixture was cooled the acid solidified, especially in the case of long chain compounds. The solid material was collected and washed well with water. The wet compound was recrystallized from 95% ethanol. The purity of

Table IV. *Physical data for mono 2-alkylacylglycerols*

R	R'	Yield*	mp °C	Analyses
C ₁₀ H ₂₁	C ₄ H ₉	64	—	Calcd: C 69.05 H 11.59 Found: C 68.5 H 11.5
C ₁₀ H ₂₁	C ₁₀ H ₂₁	67	29.5–30.5	Calcd: C 72.41 H 12.15 Found: C 72.8 H 12.6
C ₁₆ H ₃₃	C ₄ H ₉	73	r.t.	Calcd: C 72.41 H 12.15 Found: C 72.2 H 12.1
C ₁₆ H ₃₃	C ₁₀ H ₂₁	57	30.0–30.5	Calcd: C 74.64 H 12.53 Found: C 74.2 H 12.9
C ₁₆ H ₃₃	C ₁₆ H ₃₃	61	50.0–51.0	Calcd: C 76.23 H 12.79 Found: C 75.9 H 13.0

* Total yield from acid chloride.

the compounds was determined with GC on their methyl esters. For physical data of the prepared 2-alkyl fatty acids see Table III.

Preparation of mono 2-alkylacylglycerol. General procedure. Monglycerides were prepared according to Jensen and Pitas [13] with minor modifications. Acid chlorides were synthesized from the branched fatty acids and thionyl chloride. The compounds were used in acylation reactions without purification.

Acylation of 1,2-isopropylidene glycerol. 1,2-Isopropylidene glycerol (0.125 mol) and 0.1 mol of anhydrous pyridine were dissolved in 500 ml of anhydrous toluene and 0.1 mol of acid chloride was added dropwise with stirring at room temperature. The mixture was stirred for 20 h. The solution was washed with water and dried over MgSO₄. After filtration the mixture was passed through a column with neutral alumina (100 g/0.1 mol of acyl isopropylidene glycerol). The column was washed with about 350 ml of toluene. The combined organic solutions were evaporated and dried in vacuum (2 mm Hg) at about 60°C for 4–5 h.

Cleavage of the ketalgroup. The dried product from above was dissolved in methoxyethanol (300 ml/0.1 mol acylisopropylidene glycerol). Boric acid was added (100 g/0.1 mol acylisopropylidene glycerol) and the mixture was stirred for 3 h at 90–100°C. After cooling, the reaction mixture was poured onto 400 ml of water and 600 ml of chloroform was added. The mixture was vigorously shaken and precipitated boric acid was filtered. The chloroform phase was separated and washed with water, dried and evaporated. Products were identified with ¹H NMR [14, 27] and mass spectra [26]. Yield and physical data in Table IV.

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Enolate Anions from Lipid Derivatives. Alkylation of Acylisopropylidene Glycerols

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ABSTRACT

The enolate anions from isopropylidene protected monoacylglycerols have been successfully alkylated with alkyl iodides of various chain length. From these products the corresponding monoacylglycerols and triacylglycerols can be prepared. This is exemplified by the synthesis of 2-butyldodecanoyl-didodecanoyl glycerol, di-2-butyldodecanoyl-dodecanoyl glycerol and tri-2-butyldodecanoyl glycerol.

INTRODUCTION

Branched mono- and triacylglycerols are potentially interesting for industrial use, because they have physical properties different from the corresponding straight chain analogues. For example, the 2-alkyl-branched monoacylglycerols have superior surface active properties compared to the straight chain compounds (2).

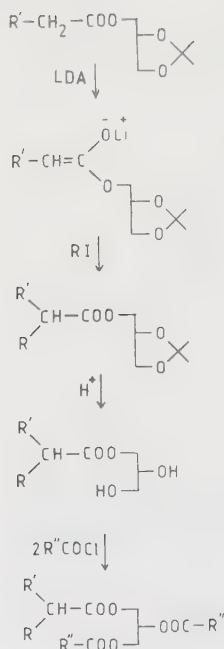
In a previous paper (1) we described the preparation of 2-alkyl-branched monoacylglycerols from the corresponding 2-alkyl-branched fatty acids. We now present the preparation of such monoacylglycerols directly from the acylisopropylidene glycerols through alkylation of their enolate anions. Cleavage of the isopropylidene group gives the monoacylglycerol, which can be acylated with acid chlorides to give branched triacylglycerols (Scheme 1). We have studied how different chain length of the monoglyceride and of the alkylating agent influence the product yields. We also have compared the efficiency of the direct alkylation method presented here, with the multistep route (1).

The preparation and alkylation of ester enolate anions has been well studied (3-14), and has been reviewed by Petragani and Yonashiro (15). One problem with this type of reactions is the tendency of enolate anions to undergo self-condensation to form the corresponding β -ketoesters (3,7). This side reaction can, however, be suppressed by the

use of a low reaction temperature (-70°C) during anion preparation. Rathke and coworkers (3) have shown that even though the amount of self-condensation product is large when the anions are generated at 0°C, anions prepared at -70°C are stable even at room temperature. They also have shown that the alkylation of lithio-*t*-butylacetate is successful, while a mixture of condensation and alkylation products is obtained with lithio ethyl acetate. Furthermore, they found that lithio ethyl hexanoate could be alkylated in good yields. Thus, it seems that a long alkyl chain in the acid part and a bulky alcohol part favor alkylation compared to side reactions. If the α -position is sterically hindered, for instance through alkyl groups in the β -position, it is even possible to prepare and alkylate the enolate anion at 0°C without condensation (6). The product yields also are dependent on the temperature and the solvent used in the alkylation step. Addition of the enolates to the alkylating agent in a mixture of tetrahydrofuran and dimethylsulfoxide at room temperature gives the best yields, according to Rathke (3), while Cregge and his coworkers (4) suggest that direct addition of the alkyl halide in THF/HMPA to the enolate at -70°C is better. On the other hand, MacPhee and Dubois (6) have found that alkylation is slow at -70°C, and that the reaction mixtures should reach room temperature before work-up. They also have reported that changing the alkylating agent from methyl to ethyl to isopropyl iodide has little effect on the yield, in the alkylation of an ester with a secondary α -carbon.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer. ^1H NMR



spectra were recorded on a Jeol MH-100 NMR spectrometer. Mass spectra were obtained using a Finnigan 4021 mass spectrometer operating at 70 eV. Gas chromatographic analyses were performed on a Varian 3700 or a Varian 1400 gas chromatograph equipped with a flame ionization detector. The columns used were a 2.5 m column of 3% OV17 on Varaport 30, 100-120 mesh, a 0.5 m column of 5% OV101 on Gaschrom Q, 100-120 mesh, and a 0.5 m glass column of 1.5% OV1 on Gaschrom Q. Elemental micro analyses were performed at Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

All alkylation reactions were carried out in an atmosphere of dry nitrogen. THF was dried by refluxing over sodium followed by distillation under nitrogen. Diisopropylamine and dimethylsulfoxide were distilled from calcium hydride and were stored over molecular sieves. Alkyl iodides were purchased from Fluka and Aldrich and were used without purification.

Butanoyl-, dodecanoyl- and octadecanoylisopropylidene glycerols were prepared through standard procedures (1,18) from the acid chlorides and isopropylidene glycerol.

General Procedures for the Alkylation of Isopropylidene Glycerols

Alkylation of butanoyl and dodecanoylisopropylidene glycerols. To 12.1 g (0.12 mol) of dry diisopropylamine in 100 ml of dry THF at 0°C, 73 ml (0.11 mol) of 1.51 M butyllithium in hexane was added. The mixture was stirred at 0°C for 15 min and then cooled to -70°C. A solution of

the acylisopropylidene glycerol (0.1 mol) in 100 ml of dry THF was added slowly, so that the temperature did not exceed -60°C. When all of the ester had been added, the clear solution was stirred at -70°C for 15 min. The cold enolate solution was then quickly transferred into a solution of the alkyl iodide (0.15 mol) in 120 ml of a 1:1 mixture of dry THF-DMSO kept at about 20°C. The yellow solution was stirred at room temperature for 15 min and then poured into ammonium hydroxide and ether. The ether phase was separated and the water solution extracted with three portions of ether. The combined ether layers were washed with ammonium hydroxide, cold diluted hydrochloric acid and finally with saturated sodium chloride. The solution was dried with MgSO₄ and evaporated. The crude product was purified through distillation or column chromatography on neutral alumina, eluting with hexane-ether mixture.

Alkylation of octadecanoylisopropylidene glycerol. As above, but the enolate was prepared at -30°C to -20°C.

All of the alkylated isopropylidene glycerols were identified by IR (1735 cm⁻¹, C=O, ester, 1370, 1380 cm⁻¹ isopropyl group), MS (*m/e* = *M*⁺-15, *M*⁺-RCOOCH₂) and ¹H NMR (CDCl₃) [δ = 0.88 ppm (t, -CH₃), δ = 1.10-1.96 ppm (m, -CH₂-), δ = 2.1-2.7 ppm (m, >CHCO), δ = 1.36 ppm (s, -CH₃), δ = 1.43 ppm (s, -CH₃), δ = 3.62-3.88 ppm (m, >CH-O), δ = 3.94-4.46 ppm (m, -CH₂-O) and also δ = 1.14 ppm (d, -CH₃) in the methyl branched analogues].

Satisfactory elemental analyses were obtained for all 2-alkyl branched acylisopropylidene glycerols. The GLC purity of the compounds was determined against an internal standard (tridecane or eicosane) and found to be at least 95%. On TLC they gave one single spot.

Yields and physical data for the compounds synthesized are summarized in Table I.

Synthesis of Triacylglycerols

2-Butyldodecanoyl monoglyceride was prepared as previously described (1). 2-Butyldodecanoyl-didodecanoyl glycerol, mp 31.0-32.0°C, di-2-butyldodecanoyl-dodecanoyl glycerol and tri-2-butyldodecanoyl glycerol (2) were prepared according to standard procedures (18) in 30-80% isolated yield. The new triacylglycerols were characterized on the basis of satisfactory elemental and spectroscopic analyses. ¹H NMR (CDCl₃): δ = 0.88 ppm (t, -CH₃), δ = 1.1-1.9 ppm (m, -CH₂-), δ = 2.16-2.50 ppm (m, -CH₂-CO, >CHCO), δ = 4.0-4.5 ppm (m, -CH₂-O), δ = 5.0-5.5 ppm (m, >CH-O).

RESULTS AND DISCUSSION

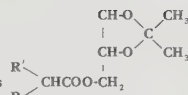
In the present study we chose butanoyl-, dodecanoyl- and octadecanoyl-isopropylidene glycerols as representatives for short-, medium- and long-chain glycerol esters, and as alkylating agent we used methyl, butyl, decyl and hexadecyl iodide. In order to find suitable conditions for anion formation and alkylation, we studied the influence of some variables (19) on the product yield, when butanoylisopropylidene glycerol was alkylated with methyl iodide in THF. In a fractional factorial design (16,17), we found that among these variables, the one that seemed to have the most important influence on the yield was the temperature of the alkylating agent. The best result was obtained when we used lithium diisopropyl amide (LDA) as base, prepared the enolate at -70°C for 15 min and quickly transferred the cold enolate to a solution of the methyl iodide in THF at room temperature. The GLC yield determined with internal standard was then 88%. Pure 2-methylbutanoylisopropylidene glycerol was isolated through distillation in 65% yield. When the same reaction conditions as above were used in the alkylation with butyl iodide, the GLC yield of 2-ethylhexanoylisopropylidene glycerol dropped to 45%. However,

TABLE I

Isolated Yields and Physical Data for 2-Alkyl-branched Isopropylidene Glycerols

Isopropylidene glycerol	R	R'	GLC yield (%)	Isolated yield (%)	Mp °C Bp °C/mmHg	n _D
2-Methyl-butanoyl-	CH ₃ -	C ₂ H ₅ -	88	65	93.5-96/4	1.4280 ^{23,5}
2-Ethyl-hexanoyl-	C ₄ H ₉ -	C ₂ H ₅ -	70	63	95.0-100.0/1	1.4348 ²¹
2-Ethyl-dodecanoyl-	C ₁₀ H ₂₁ -	C ₂ H ₅ -	67	60	126-134/5-10 ⁻²	1.4450 ^{23,5}
2-Ethyl-octadecanoyl-	C ₁₆ H ₃₃ -	C ₂ H ₅ -	66	60	oil	1.4487 ^{23,5}
2-Methyl-dodecanoyl-	CH ₃ -	C ₁₀ H ₂₁ -	89	73	128-130/5-10 ⁻²	1.4425 ^{23,5}
2-Butyl-dodecanoyl-	C ₄ H ₉ -	C ₁₀ H ₂₁ -	72	65	oil	1.4450 ^{23,5}
2-Decyl-dodecanoyl-	C ₁₀ H ₂₁ -	C ₁₀ H ₂₁ -	64	53	oil	1.4498 ^{23,5}
2-Methyl-octadecanoyl-	CH ₃ -	C ₁₆ H ₃₃ -	76	50	oil	1.4489 ^{23,5}
2-Butyl-octadecanoyl-	C ₄ H ₉ -	C ₁₆ H ₃₃ -	63	53	25	—
2-Decyl-octadecanoyl-	C ₁₀ H ₂₁ -	C ₁₆ H ₃₃ -	63	45	35.0-36.0	—
2-Hexadecyl-octadecanoyl-	C ₁₆ H ₃₃ -	C ₁₆ H ₃₃ -	51	41	54.5-56.5	—

GLC yield of alkylated product determined with tridecane or eicosane as internal standard.



the yield was raised to 70% by the use of THF/DMSO as solvent in the alkylation step. Further elongation of the chain in the alkyl iodide gave somewhat lower yields, as shown in Table I. On changing the ester from butanoyl-isopropylidene glycerol to dodecanoyl-isopropylidene glycerol, we observed no different behavior: the GLC yield for methylation was 89%, with a slight decrease of the yield as the chain length of the iodide is increasing. For the long chain octadecanoyl-isopropylidene glycerol the GLC yields as a whole are lower, but the same tendency still remains within the series of alkyl halides. This lower yield could be a consequence of the much lower solubility of the starting glycerol in THF at -70 °C. To be able to dissolve this compound, we had to raise the temperature to -30 to -20 °C and prepare the enolate anion at this temperature. In this case it thus seems that this variable is of some importance for the product yield. Although the yields are lower, it is possible to prepare the very long chain 2-hexadecyloctadecanoyl-isopropylidene glycerol in 41% isolated yield. All of the compounds in Table I were isolated through distillation or column chromatography in yields ranging from 41 to 73%. Acidic cleavage of the ketal group gives the 2-alkyl branched monoglycerides. The total yield of monoacylglycerols prepared via this reaction path is about 35%, based on the straight chain free fatty acids. This may be compared to the overall yield of about 20% that we obtained in the sequence used in our previous work (1). The possibility of using the same starting material in many different alkylations constitutes another advantage of the direct alkylation of acylisopropylidene glycerols. Triacylglycerols can be prepared from the branched monoacylglycerols through acylation with acid chlorides. As examples, we have prepared the mono-2-butyl-dodecanoyl-di-dodecanoyl glycerol, the di-2-butyl-dodecanoyl-dodecanoyl glycerol and the tri-2-butyl-dodecanoyl glycerol. As can be expected, the branched triacylglycerols have lower melting points than the saturated straight chain analogues with the same carbon number. One example is tri-2-butyl-dodecanoyl glycerol (C₄₈), which is an oil at -50 °C, while trihexadecanoyl glycerol (C₄₈, tripalmitin) melts at 66 °C. This lowered melting point might be of

importance in the search for liquid lubricating oils with high stability towards oxidation.

ACKNOWLEDGMENTS

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- Variables: base (lithium diisopropylamide or lithium cyclohexylisopropylamide), reaction temperature and time at the formation of enolate, mode of addition (direct or inverse) of methyl iodide, temperature of the enolate and alkylating agent, addition rate on alkylation.

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Synthesis of 2-Phenylthio, 2-Phenylseleno and 2-Carbomethoxy Acyl Isopropylidene Glycerols and the Corresponding Triacylglycerols

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Abstract

Enolate anions from acyl isopropylidene glycerols have been prepared. Treatment of these anions with various electrophiles, i.e. diphenyl disulfide, diphenyl diselenide, carbon dioxide and methyl chloroformate, give new 2-substituted protected monoacylglycerols. Acidic cleavage of the isopropylidene group gives the monoglyceride, which can be acylated to give the corresponding triacylglycerols. This is exemplified by the synthesis of didodecanoyl-2-phenylthiododecanoyl-glycerol and didodecanoyl-2-phenylselenododecanoyl-glycerol, which have been prepared and purified. In contrast, the preparation of 2-carbomethoxydodecanoyldidodecanoyl glycerol from 2-carbomethoxydodecanoylisopropylidene glycerol was complicated.

Introduction

Triglycerides with various substituents in the α -position of the carboxylic acid chain are potentially interesting for industrial use, since triglycerides from plants constitute a renewable source of raw material of great importance. In an earlier paper [1] we described the preparation of lithium enolate anions from acylisopropylidene glycerols and their alkylation with alkyl halides. We have now extended this work to the reactions of such enolates with disulfides, diselenides and carboxylating agents.

The reaction of enolates from ketones and esters with sulfonylating agents to give α -thio-substituted products provides a convenient route to the synthesis of α,β -unsaturated compounds under mild conditions, and has been extensively studied [2–8]. The success of the sulfonylation depends on the reactivity of both the enolate anion and of the thiolation reagent. While the dianion of a carboxylic acid reacts even with elemental sulfur, the less reactive ketone enolate needs a more reactive electrophile, such as diphenyl disulfide [6]. The reactivity of ester enolates falls in between these two categories, and depending on the ester group, high yields of 2-methylthio and 2-phenylthio esters can be obtained by reaction with dimethyl disulfide and the more reactive diphenyl disulfide. For example, Trost and Salzmann [27] have shown that the methyl and ethyl esters of linoleic acid give lower yields of the 2-methylthio esters than does the *t*-butyl ester at 0 °C. They also found that long reaction times caused desulfonylation back to the starting ester. Other drawbacks of this reaction are the possibility of proton transfer from the more acidic α -sulfonylated product to unreacted enolate anion leading to desulfonylation, and the possibility for the remaining enolate

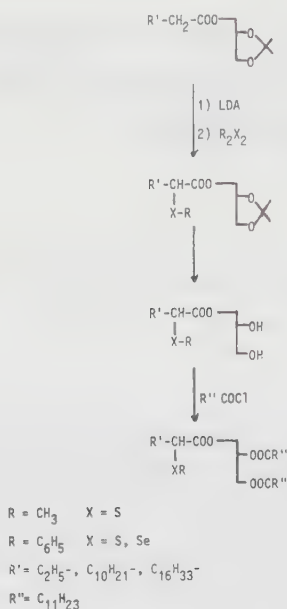
anions to add to the α -sulfonylated ester leading to the condensation product. It has also been shown in the literature [9] that lithium thiomethylate is capable of cleaving esters, a reaction that leads to the formation of other by-products. As shown by Trost and his co-workers [3], the yield and purity of the product can be enhanced by changing the solvent from THF to THF-HMPA mixtures, or by changing the electrophile from dimethyl disulfide to diphenyl disulfide.

In the same manner as above, the α -selenyl compounds can be synthesized from ester enolates by reaction with diphenyl diselenide or phenylselenenyl halides [5, 10, 11]. Another more complicated route to the 2-phenylselenenyl esters involves nucleophilic displacement in the α -haloester by phenylselenenolate anion [12]. Oxidation and elimination of the seleno compound give, as in the case of the sulfur compound, the α,β -unsaturated ester under mild conditions.

The reaction of ester enolate anions with carbon dioxide offers a way to introduce polarity into the molecule [13]. Such malonic acid derivatives can also be obtained from the dianion of the carboxylic acid by reaction with alkyl chloroformates or dialkyl carbonates [14]. The reaction of ester enolates with alkyl chloroformates or dialkyl carbonates affords a direct method to mixed malonic esters. These compounds can of course also be prepared by ordinary alkylation of malonic esters [15], or via reactions of carboxylic esters with oxalates [16], but these methods do not appear to be as convenient as the direct carboxylation.

Results and discussion

As in our previous study [1], we chose butanoyl-, dodecanoyl- and octadecanoyl-isopropylidene glycerols as starting materials. The enolate anions were prepared as before by the action of lithium diisopropylamide in THF at –70 °C, except in the case of octadecanoylisopropylidene glycerol where the temperature was held at –30 °C to –40 °C. At first we attempted to prepare the methylthio compounds from the enolates (Scheme 1). According to GLC/MS, it was found that the desired products were formed in low and decreasing yields with increasing chain length of the isopropylidene glycerols. For comparison, we reacted ethyl hexanoate and methyl dodecanoate with dimethyl disulfide. From the GLC distribution in Table I it can be seen that the ethyl methylthiohexanoate is successfully formed, while the amount of product



Scheme 1

Table I. Reaction of ester enolates with dimethyl disulfide: GLC distribution (%)

Enolate	GLC distribution (%)		
	Starting material	Product	By-products
Ethyl hexanoate	—	87	13
Methyl dodecanoate	21	47	32
Butanoylisopropylidene glycerol	15	47	38
Dodecanoylisopropylidene glycerol	13	26	61
Octadecanoylisopropylidene glycerol	13	21	66

is considerably less in the case of methyl dodecanoate. It also seems that the reactivities of methyl dodecanoate and butanoylisopropylidene glycerol are comparable in this reaction. In accordance with Trost's work [3], a change of the electrophile to diphenyl disulfide gives higher yields of the sulfenylated ester, but as shown in Table II, the isolated yields of the pure products are not very high. Furthermore, an increase in the length of the acyl chain is followed by a decrease in the product yield. This is also true for the reaction of the enolates with diphenyl diselenide.

From 2-phenylthiododecanoyl isopropylidene glycerol and 2-phenylselenododecanoyl isopropylidene glycerol, the mono-glycerides were obtained by boric acid cleavage of the isopropylidene group [17]. Acylation [18] with dodecanoyl chloride gave the triacyl glycerols containing one 2-substituted acyl group (Scheme 1). With these compounds it should be possible to introduce unsaturation into the triacyl glycerols.

The mass spectra of the 2-phenylthio and the 2-phenylseleno

triacylglycerols at 70 eV both show molecular ions with relative intensities that are comparable to the intensities obtained from the fragments in which one acyloxy group is cleaved off (1–10 rel. %). This is rather unusual for triacylglycerols, for which molecular ions are often missing or have very low relative abundance (0.2 rel. %), and M^+ -acyloxy fragments are often most common [19].

As mentioned above, both the 2-carboxy- and the 2-carbomethoxy acyl isopropylidene glycerols are accessible through a direct reaction with the ester enolates [14]. The 2-carbomethoxy derivative can also be obtained through esterification of the 2-carboxylic acid derivative with methyl iodide in acetone in the presence of potassium carbonate [20]. The reactions are shown in Scheme 2. We have used both methods to prepare the 2-carboxymethylated acylisopropylidene glycerols, and the isolated yields are shown in Table II. The crude carboxylated acylisopropylidene glycerols were transformed to the methyl esters, which were purified by column chromatography. As can be seen, the total isolated yields of the carboxymethylated products are about the same, irrespective of which synthetic method we used. Nevertheless, the stepwise procedure gives a more easily purified product since the carboxylated acylisopropylidene glycerol is removed from the starting material by extraction. From carbomethoxydodecanoylisopropylidene glycerol we prepared the corresponding monoacyl glycerol, which was acylated with dodecanoyl chloride. According to GLC we found that three compounds were formed in the proportions 1.2:1.7:1.0. By column chromatography and preparative TLC we achieved poor separation of the components, and no pure product could be isolated. After analysis by chemical ionization mass spectrometry with ammonia as reagent gas [21], possible structures for two of the compounds could be proposed. The molecular ion for the compound that gives the dominant peak in GLC is consistent with the expected 2-carbomethoxydodecanoyldidodecanoyl glycerol. One of the by-products gives a molecular ion that probably corresponds to didodecanoyl glycerol. The third component in the mixture is still not identified.

It is not unlikely that these compounds have similar polarities, and thus are difficult to separate on, for instance silica. So far, we have not tried to do HPLC separations, but this may be a useful method. For the moment, we are not sure whether both of the by-products are formed during the acylation reaction or not. If so, it is of course possible to try other esterification methods – for instance, with dicyclohexylcarbodiimide [22] or carbonyldiimidazole [23] as condensing agents. The possibility of reacting the alkylmalonic monomers with diacyl glycerol offers another way to the 2-carbomethoxyacyl triglyceride that remains to be examined.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 spectrometer. ^1H NMR spectra were recorded on a Jeol MH 100 NMR spectrometer and mass spectra were obtained using a Finnigan 4021 mass spectrometer operating at 70 eV. Gas chromatographic analyses were performed on a Varian 3700 or a Varian 1400 gas chromatograph equipped with a flame ionization detector. The columns used were a 2.5 m stainless-steel column packed with 3% OV 17 on Varaport 30, 100–120 mesh, and a 0.5 m glass

Table II. Yields and physical data of 2-substituted acylisopropylidene glycerols

Starting isopropylidene glycerol	Electrophile	Yield	M.p. B.p.	n_D^{25}	Analyses
Butanoyl-	PhSSPh	48	—	1.5200	Calc. for: $C_{18}H_{22}O_4S$: Found: C 61.91 H 7.14 S 10.33 C 61.83 H 7.06 S 10.41
	PhSeSePh	50	—	1.5298	Calc. for: $C_{18}H_{22}O_4Se$: Found: C 53.79 H 6.21 Se 22.10 C 53.73 H 6.13 Se 22.05
	CO_2 ; H^+ ; CH_3I	85; * 56†	—	—	—
	$Cl-CO_2CH_3$	60	$97-101^{\circ}/3 \times 10^{-4}$	1.4384	Calc. for: $C_{17}H_{20}O_6$: Found: C 55.37 H 7.74 — C 55.55 H 7.79 —
Dodecanoyl-	PhSSPh	41	—	1.5003	Calc. for: $C_{24}H_{38}O_4S$: Found: C 68.21 H 9.06 S 7.59 C 68.24 H 9.12 S 7.61
	PhSeSePh	55	—	1.5092	Calc. for: $C_{24}H_{38}O_4Se$: Found: C 61.40 H 8.16 Se 16.82 C 61.54 H 8.11 Se 16.93
	CO_2 ; H^+ ; CH_3I	64; * 49†	—	1.4545	Calc. for: $C_{23}H_{34}O_6$: Found: C 63.66 H 9.56 — C 62.72 H 9.57 —
	$Cl-CO_2CH_3$	71	—	1.4467	Calc. for: $C_{20}H_{30}O_6$: Found: C 64.49 H 9.74 — C 64.51 H 9.71 —
Octadecanoyl-	PhSSPh	39	—	1.4983	Calc. for: $C_{30}H_{50}O_4S$: Found: C 71.10 H 9.95 S 6.33 C 71.04 H 9.81 S 6.41
	PhSeSePh	36	25	1.4992	Calc. for: $C_{30}H_{50}O_4Se$: Found: C 65.08 H 9.10 Se 14.26 C 65.04 H 9.02 Se 14.33
	CO_2 ; H^+ ; CH_3I	62; * 38†	47.5–48.5	—	Calc. for: $C_{28}H_{46}O_6$: Found: C 67.84 H 10.48 C 67.90 H 10.58
	$ClCO_2CH_3$	39	29–31	—	Calc. for: $C_{28}H_{46}O_6$: Found: C 68.38 H 10.59 C 68.47 H 10.69

* Yield of crude carboxylic acid.

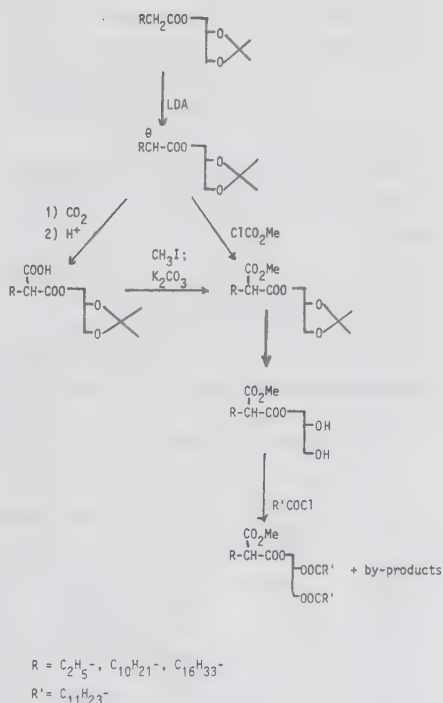
† Isolated yield of methyl ester based on straight-chain acylisopropylidene glycerol.

column packed with 1.5% OV 1 on Gaschrom Q, 100–120 mesh. Elemental micro analyses were performed at Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

All metallation reactions were carried out in an atmosphere of dry nitrogen, using the septum technique. THF was dried by refluxing over sodium followed by distillation under nitrogen. Diisopropylamine was distilled from calcium hydride and was stored over molecular sieves. Dimethyl disulfide was purchased from Merck and distilled before use. Diphenyl disulfide was obtained from Fluka and was recrystallized before use. Diphenyl diselenide was prepared according to the literature [24] and recrystallized before use. Methyl chloroformate from Fluka was used without purification. Butanoyl-, dodecanoyl- and octadecanoylisopropylidene glycerols were prepared by standard procedures [18, 25], from the acid chlorides and isopropylidene glycerol.

General procedure for the preparation of lithio enolates of acyl-isopropylidene glycerols [1, 26]

To a solution of 1.2 g (1.7 ml, 0.012 mol) of diisopropylamine in 20 ml of dry THF, 7.5 ml (0.011 mol) of butyllithium in hexane (1.46 M) was added at 0 °C. The light-yellow solution was stirred at 0 °C for 15 min and was then cooled with dry ice/ethanol to –70 °C. At that temperature 0.010 mol of the acylisopropylidene glycerol in 10 ml of THF was added with stirring. In the case of octadecanoylisopropylidene glycerol the temperature of the lithium diisopropylamide was raised to –30 to –40 °C before addition of the acetone glycerol. The resulting lithio enolates were stirred at –70 °C (–40 °C for octadecanoylisopropylidene glycerol) for 15–20 min, and were then reacted with the different electrophiles as described below.



(A) Reaction with dimethyl disulfide [3,27] to give 2-methylthioacylisopropylidene glycerols

2-Methylthiobutanoylisopropylidene glycerol. The enolate was quickly transferred through a short, cooled needle into a solution of 1.1 g (1.1 ml, 0.012 mol) of dimethyl disulfide in 10 ml of THF at -70°C . The resulting mixture was stirred at -70°C for 15 min and was then allowed to reach 0°C . The reaction mixture was poured into a mixture of saturated aqueous sodium hydrogen carbonate solution and ether. As internal standard 1.0 g of tridecane was added to the ether phase at work-up. The aqueous layer was separated and extracted with ether. The combined ether phases were washed with sodium bicarbonate and sodium chloride solutions. The organic phase was dried with anhydrous magnesium sulfate and analysed on GLC. According to this analysis the solution contained at least four components, in addition to the internal standard. GLC/MS analysis revealed that some starting material remained and that condensation products seemed to be present along with the desired product. If the GLC response factor of the product was assumed to be the same as for the starting material, the yield of 2-methylthiobutanoylisopropylidene glycerol was calculated to be 44% of the theoretical yield. The distribution of starting material, product and by-products, as determined by GLC, is given in percent in Table I. No attempts to purify the product were made.

2-Methylthiododecanoyl- and 2-methylthiooctadecanoylisopropylidene glycerol. The enolates were transferred to a solution of 1.1 g (1.1 ml, 0.012 mol) of dimethyl disulfide in 10 ml of THF kept at room temperature. The resulting mixture was stirred at this temperature for thirty minutes and was then worked up as above. In these cases no internal standard was added. Table I shows the percentages of starting material, product and by-products, as determined by GLC. The 2-methylthio compounds were identified by GLC/MS, but were not isolated.

Synthesis of ethyl 2-methylthiohexanoate and methylthiododecanoate was performed as above. The distribution of the components in the crude product (GLC) is shown in Table I.

(B) Reaction with diphenyl disulfide [3, 5] to give 2-phenylthioacylisopropylidene glycerols

2-Phenylthiobutanoyl-, 2-phenylthiododecanoyl- and 2-phenylthiooctadecanoylisopropylidene glycerol. The enolate was quickly added to a solution of 2.6 g (0.012 mol) of diphenyl

disulfide in 12 ml of THF kept at 0°C . The resulting mixture was stirred at 0°C for 15 min, allowed to reach room temperature, and was then stirred for another 15 min. The solution was worked up as before, with the addition of tridecane as internal standard. The GLC yields of the products, after determination of the response factors, were found to be 68–69% of the theoretical value in all three cases. The crude products were purified by column chromatography on neutral alumina, eluting the products with hexane-ether 9:1. Isolated yields of the products were 48%, 41% and 39%, respectively, calculated from the corresponding acylisopropylidene glycerols. Yields, physical and analytical data are collected in Tables II and III.

(C) Reaction with diphenyl diselenide [10, 11] to give 2-phenylselenobutanoyl-, 2-phenylselenododecanoyl- and 2-phenylselenooctadecanoyl-isopropylidene glycerols

To the enolates kept at -70°C (-60°C for the enolate of octadecanoylisopropylidene glycerol) 4.0 g (0.013 mol) of diphenyl diselenide dissolved in 12 ml of THF was quickly added. The mixture was stirred at -70°C (-50 to -60°C in the case of the octadecanoyl compound) for 1 h, allowed to reach room temperature and was then stirred for another 15 min. After that time the mixture was poured into cold sodium hydrogen carbonate and ether. The water layer was separated and extracted with ether. The combined ether solutions were washed with saturated sodium hydrogen carbonate, 2 M hydrochloric acid, and finally with saturated sodium chloride. The organic phase was dried with MgSO_4 and evaporated. The crude products were chromatographed on neutral alumina and were eluted with hexane and hexane-ether 7:3. Yields of the isolated products and physical data are given in Table II. Characteristic mass fragments are summarized in Table III.

^1H NMR spectra for the 2-phenylthio- and 2-phenylselenoacylisopropylidene glycerols were recorded in (CDCl_3) . The following shifts were obtained for the 2-substituted butanoyl derivatives: δ 1.0 (t, CH_3), 1.6–2.1 (m, $-\text{CH}_2-$), 3.46–3.76 (m, $-\text{CH}$), 3.46–4.34 (m, glycerol), 1.34 (s, CH_3), 1.40 (s, CH_3), 7.1–7.7 (m, phenyl). NMR data for the 2-substituted dodecanoyl and octadecanoyl derivatives: δ 0.88 (t, CH_3), 1.0–2.1 (m, $-\text{CH}_2-$), 3.46–3.78 (m, $-\text{CH}$), 3.46–4.34 (m, glycerol), 1.34 (s, CH_3), 1.40 (s, CH_3), 7.1–7.7 (m, phenyl).

Table III. MS fragments of 2-phenylthio- and 2-phenylseleno-acylisopropylidene glycerols

Isopropylidene glycerol	M^+ m/e (rel. %)	M^+-CH_3 m/e (rel. %)	$\text{M}^+-\text{CH}_2\text{COCH}_3$ m/e (rel. %)	RCOOH m/e (rel. %)	R-X  m/e (rel. %)	 m/e (rel. %)	C_3H_7^+ m/e (rel. %)
2-phenylthio-							
butanoyl-	310 (10)	295 (15)	252 (0.5)	196 (19)	151 (100)	101 (61)	55 (47)
dodecanoyl-	422 (2)	407 (2)	364 (0.8)	308 (4)	263 (3)	101 (8)	55 (100)
octadecanoyl-	506 (0.5)	491 (2)	448 (0.3)	392 (3)	347 (4)	101 (26)	55 (100)
2-phenylseleno-							
butanoyl-	358 (9)	343 (9)	—	244 (12)	199 (21)	101 (88)	55 (100)
dodecanoyl-	470 (0.1)	455 (0.1)	—	356 (0.3)	311 (0.1)	101 (21)	55 (100)
octadecanoyl-	554 (1)	539 (1)	496 (0.2)	440 (1)	395 (1)	101 (33)	55 (100)

(D) Reaction with dry ice to give 2-carboxybutanoyl-, 2-carboxydodecanoyl- and 2-carboxyoctadecanoyl-isopropylidene glycerols [13]

The enolates prepared as above were poured into an excess of fresh dry ice covered with dry ether. When all of the carbon dioxide had evaporated, the ether solution was diluted with water and was carefully acidified. The organic layer was separated and the water phase was extracted with ether.

In the case of butanoylacetone glycerols, several ether extractions were necessary since the product seems to be somewhat soluble in water. The combined ether phase was then extracted with saturated sodium bicarbonate and with 2 M sodium hydroxide. In the case of long-chain products the carboxylate was obtained as an oily phase between the organic phase and the alkaline water phase. The carboxylic acid was recovered by careful acidification with ice-cooling and in the presence of ether. The acidic water layer was quickly extracted with several portions of ether. The combined ether solutions were washed with ice-water and dried with MgSO_4 . The crude products were obtained after evaporation, and were transformed to the corresponding methyl esters without further purification.

Analytical samples of 2-carboxydodecanoyl-isopropylidene glycerol were obtained by recrystallization in hexane at -20°C , and of 2-carboxyoctadecanoyl-isopropylidene glycerol by recrystallization from ethanol at -20°C . Yields and physical data are given in Table II.

Preparation of 2-carbomethoxybutanoyl-, 2-carbomethoxydodecanoyl- and 2-carbomethoxyoctadecanoyl-isopropylidene glycerols [20]

These glycerols were obtained by dissolving the crude carboxy derivatives from above in acetone (5 ml/mmol acyl isopropylidene glycerol) and adding solid potassium carbonate (1 equiv) and methyl iodide (3 equiv). The mixtures were refluxed gently over night. After cooling with ice-water, the precipitates were filtered off and were washed with cold acetone. The filtrates were evaporated and the residues dissolved in ether. The ether phases were washed with water until neutral, dried with magnesium sulfate and evaporated. The crude products were purified by flash chromatography [28] on silica, eluting the product with hexane-ether, 7:3. Total yields of the carbomethoxyacylisopropylidene glycerols are given in Table II.

(E) Reaction with methyl chloroformate to give 2-carbomethoxybutanoyl-, 2-carbomethoxydodecanoyl- and 2-carbomethoxyoctadecanoyl-isopropylidene glycerols [14]

The enolate, kept at -70°C (at -40°C for octadecanoyl-acetone glycerol), was quickly added to a solution of 1.1 g (0.93 ml, 0.012 mol) of methyl chloroformate in 10 ml of THF

at -70°C (-40°C). The mixture was stirred for 20 min and then poured into ice-cold dilute hydrochloric acid and ether. The water layer was separated and extracted with ether. The combined ether solutions were washed with aqueous sodium bicarbonate and saturated brine. Drying with MgSO_4 and evaporation gave crude carbomethoxyacylisopropylidene glycerols. Flash chromatography on silica [28] gave the pure products after elution with hexane-ether, 7:3. Yields and analyses are presented in Table II. Characteristic mass fragments are summarized in Table IV.

^1H NMR (in CDCl_3): 2-carbomethoxybutanoylisopropylidene glycerol: δ 0.96 (t, CH_3), 1.94 (p; CH_2), 3.33 (t, $-\text{CH}$), 3.62–4.50 (m, glycerol), 1.35 (s, CH_3), 1.41 (s, CH_3), 3.72 (s, $-\text{OCH}_3$).

The NMR spectra of the 2-carbomethoxydodecanoyl- and 2-carbomethoxyoctadecanoyl isopropylidene glycerols are very similar and have the following shifts (CDCl_3): δ 0.87 (t, CH_3), 1.1–2.1 (m, $-\text{CH}_2-$), 3.38 (t, $-\text{CH}-$), 3.60–4.50 (m, glycerol), 1.35 (s, CH_3), 1.41 (s, CH_3), 3.72 (s, $-\text{OCH}_3$).

Synthesis of mono-2-phenylthio- and mono-2-phenylseleno- and mono-2-carbomethoxy-dodecanoyl glycerols [17]

A mixture of 0.005 mol of the 2-substituted acylisopropylidene glycerol and 5 g of boric acid in 15 ml of methoxyethanol was heated to 90 – 100°C for 3 h. After cooling, the mixture was poured into chloroform and water. The product was shaken for several minutes and was filtered by suction. The chloroform layer was separated and washed with water. Drying with sodium sulfate and evaporation gave the crude mono-acyl glycerols in 83–94% yield. The monoglycerides were acylated without purification.

Synthesis of didodecanoyl-2-phenylthiododecanoyl glycerol and didodecanoyl-2-phenylselenododecanoyl glycerol

The monoglyceride (1 equiv) and dry pyridine (3 equiv) were dissolved in dry methylene chloride (5 ml/mmol monoglyceride). Dodecanoyl chloride (1.2 equiv/hydroxyl in the monoglyceride) was added with stirring. The reaction mixture was stirred at room temperature for 3 days. After that time ether and water were added. The ether layer was separated and washed with water. The solution was dried with magnesium sulfate and evaporated. The crude product was filtered through a short column packed with neutral alumina and eluted with hexane-ether, 7:3. Flash chromatography on silica gave the pure triacyl glycerols after elution with hexane-ether, 9:1.

Didodecanoyl-2-phenylthiododecanoyl glycerol was obtained in 60% isolated yield. Characteristic mass fragments: 746 (M^+), 547 (M^+ -acyloxy), 439 (M^+ -acyloxy).

Table IV. MS fragments of 2-carbomethoxyacylisopropylidene glycerols

Isopropylidene glycerol	$\text{M}^+ - \text{CH}_3$	$\text{M}^+ - \text{CH}_3\text{COCH}_3$	$\text{M}^+ \left\{ \begin{array}{l} -\text{CH}_2\text{COCH}_2 - \text{RCO} \\ -\text{OCH}_3 \end{array} \right.$		
	m/e (rel. %)	m/e (rel. %)	m/e (rel. %)	m/e (rel. %)	m/e (rel. %)
2-carbomethoxy-					
butanoyl-	245 (9)	202 (0.5)	171 (4)	129 (29)	101 (32)
dodecanoyl-	357 (14)	314 (0.5)	283 (1)	241 (2)	101 (100)
octadecanoyl-	441 (10)	398 (1)	367 (0.4)	325 (1)	101 (98)
					59 (100)
					55 (100)
					57 (100)

NMR (CDCl_3): δ 0.90 (t, $-\text{CH}_3$), 1.2–2.0 (m, $-\text{CH}_2-$), 2.3 (t, $-\text{CH}_2-\text{CO}-$), 3.62 (t, $-\text{CH}-$), 3.84–4.52 (m, glycerol), 5.02–5.38 (m, glycerol), 7.2–7.6 (m, phenyl).
 Anal. found: C 72.25; H 10.62; S 4.28. Calc. for $\text{C}_{15}\text{H}_{18}\text{O}_6\text{S}$: C 72.34; H 10.52; S 4.29.

Didodecanoyl-2-phenylselenododecanoyl glycerol was obtained in 50% isolated yield. Characteristic mass fragments: 794 (M^+), 595 ($\text{M}^+ - \text{acyloxy}$), 439 ($\text{M}^+ - \text{acyloxy}$).

NMR (CDCl_3): δ 0.90 (t, $-\text{CH}_3$), 1.1–2.0 (m, $-\text{CH}_2-$), 2.3 (t, $-\text{CH}_2-\text{CO}-$), 3.58 (t, $-\text{CH}-$), 3.80–4.40 (m, glycerol), 5.02–5.40 (m, glycerol), 7.1–7.7 (m, phenyl).
 Anal. found: C 68.29; H 9.90; Se 10.04. Calc. for $\text{C}_{35}\text{H}_{78}\text{O}_6\text{Se}$: C 68.07; H 9.90; Se 9.94.

Synthesis of 2-carbomethoxydodecanoyl-didodecanoyl glycerol

The monoacylglycerol, 1.0 g (0.003 mol) and 0.7 g (0.7 ml, 0.009 mol) of dry pyridine were dissolved in 15 ml of dry methylene chloride. To this solution, 1.6 g (0.007 mol) of dodecanoyl chloride was added with stirring. The mixture was stirred at room temperature for 3 days and was then worked up as above. GLC on the crude product gave three dominant peaks in the proportions 1.2 : 1.7 : 1.0. Column chromatography on alumina followed by flash chromatography on silica and preparative TLC gave poor separation, and no pure product was obtained. GLC/MS on the product mixture gives no certain identification of the carbomethoxytriacyl glycerol. Chemical ionization [21] with ammonia as the reagent gas shows that the desired triacyl glycerol is present in the mixture ($\text{M}^+ = 714$; molecular ion + ammonium ion), together with other components, one of which probably is the didodecanoyl glycerol ($\text{M}^+ = 472$; molecular ion + ammonium ion). Obviously these products show similar or identical chromatographic behaviour.

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Synthesis of Trimethylsilyl Ketene Acetals from Triacyl Glycerols
and their Reaction with t-Butyl Chloride and 1-Adamantyl Bromide

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Abstract

The trimethylsilyl ketene acetals of tributanoyl glycerol and tridodecanoyl glycerol have been prepared by treatment with a cooled mixture of lithium diisopropyl amide and trimethylsilyl chloride. From the trimethylsilyl ketene acetals the α -t-alkylated triacyl glycerols were obtained by reaction with t-butyl chloride and 1-adamantyl bromide in the presence of zinc chloride. In some cases mixed α -alkylated and α -silylated triacyl glycerols were obtained. The α -trimethylsilyl groups are probably introduced by rearrangement of the trimethylsilyl ketene acetals. We observed such rearrangements when we treated the trimethylsilyl ketene acetals of tributanoyl glycerol and tridodecanoyl glycerol with zinc chloride in the absence of alkylating agent.

Introduction

Triacyl glycerols from plants are an important source of renewable raw material. The usefulness of triacyl glycerols for industrial purposes would be even greater if well defined chemical modifications, leading to compounds with different properties, were possible [1]. For several years, we have been studying reactions of enolate anions of lipid derivatives [2-4]. So far we have been working with protected fatty acids and monoglycerides as starting materials. After alkylation of anions derived from these compounds, the corresponding triacyl glycerols were prepared. In this paper we describe alkylations in which the triglycerides are used as starting materials.

The usual problem involved in reactions of ester enolate anions is the tendency toward self condensation [5]. When enolate anions of triacyl glycerols are prepared, this side reaction can be expected to be more pronounced, since we always have three acyl residues bonded together, and thus a possibility for internal self condensation. To avoid this, we wanted a way to prepare the enolate anions in the presence of a reactive electrophile, which was supposed to trap the anion before condensation took place. One very reactive electrophile is found in trimethylsilyl chloride, which gives the O-trimethylsilyl ketene acetal on reaction with ester enolates (Fig. 1) [6,7]. Some C-silylation is also observed. Usually the trimethylsilyl ketene acetal is obtained after the addition of trimethylsilyl chloride (TMSCl) to a solution of the enolate anion [7].

However Corey and Gross [8] have shown that lithium diisopropylamide (LDA) is compatible with TMSCl at -70°C . It is thus possible to prepare ester enolate anions in the presence of TMSCl. The immediate trapping of the anions by TMSCl makes self condensation less probable. The trimethylsilyl ketene acetals are rather stable compounds that can be isolated and handled as long as moisture and acids are avoided. It is usually possible to distill them but they react at higher temperatures to give addition products [6,7]. Once the trimethylsilyl ketene acetals are prepared a variety of reactions is accessible. Some examples are α -t-alkylations [9-12], α -acylations [13], aldol additions [14,15], Michael additions [16,17] and oxidations [18]. It is also possible to introduce alkenes and alkanes in the α -position through alkylation with the phenylsulfinyl chloride adduct of alkenes [19,20].

In this paper we describe the preparation of trimethylsilyl ketene acetals from triacyl glycerols and their alkylation with t-alkyl halides in the presence of Lewis acids.

Results and discussion

In our work we have used tributanoyl glycerol and tridodecanoyl glycerol as starting materials for anion production. Since all our attempts to α -butylate, α -carboxylate and α -deuteriate the trienolate anions of these triacyl glycerols under basic conditions [21] were unsuccessful, we turned our interest to the two step procedure of α -alkylation via the O-silylated anions (Scheme 1). To prepare the ketene acetals we chose the method described by Corey and Gross [8], in which the ester, in our case the triacyl glycerol, is added to a cooled mixture of LDA and TMSCl in THF (method A in Tables I and II). When the triacylglycerol had been added, the silyl ketene acetal was isolated by evaporation under nitrogen, dissolved in CH_2Cl_2 or CHCl_3 , filtered and used in further reactions (see below) without purification. We have studied this reaction with different amounts of LDA, to find out whether or not selective enolization of the different acyl groups in the triacyl glycerol was possible. The resulting trimethylsilyl ketene acetal solutions were analyzed by ^1H NMR. Tables I and II show the ^1H NMR shifts obtained for the products formed in the reaction of tributanoyl glycerol respective tridodecanoyl glycerol. The ^1H NMR shifts for the unreacted triacyl glycerols are given as reference. Some general results may be noted. First, the protons of the acyl residues of the unreacted triacyl glycerols show a small difference in shifts depending on the position of esterification in the glycerol. The protons in the acyl residues attached to the 1- and 3-positions of glycerol

tend to show resonance at lower frequency than those in the acyl group esterified at the 2-position [34]. In tributanoyl glycerol this is true for all of the protons in the acyl groups, but in tridodecanoyl glycerol only for the protons in the α -position of the acyl residue. The same tendency is observed in the trimethylsilyl ketene acetals. The second general observation is that the vinyl protons in all of the silyl ketene acetals prepared show resonance at 3.64 ppm. According to the literature [15,22,23], this is consistent with formation of the E-form of the silyl ketene acetals, the expected isomer when the reaction is kinetically controlled. The preference for formation of the E-silyl ketene acetal can be explained in terms of smaller steric interactions [8] in the E-transition state, than in that for the thermodynamically stable Z-form (Fig. 2) [22]. The bulkier the base and the R group, the more favoured the E-form would seem to be.

The reaction of tributanoyl glycerol with two equivalents of LDA per acyl group (method A) followed by TMSCl led to complete formation of the trimethylsilyl ketene acetal with three OTMS groups. This is demonstrated in ^1H NMR by the complete absence of α -acyl protons ($\delta = 2.3$ ppm), and of the β -methylene protons at $\delta = 1.65$ ppm and 1.66 ppm. Instead, we see vinyl protons at $\delta = 3.64$ ppm and β -methylene protons at $\delta = 1.97$ ppm and $\delta = 1.99$ ppm. Furthermore, the glycerol part of the spectrum is completely different from that of tributanoyl glycerol. The silyl ketene acetal gives an A_4X spectrum instead of the usually observed AA'BB'X spectrum of triacyl glycerols. With smaller amounts of LDA (1 equiv./acyl group), the spectrum

of the silyl ketene acetal is a combination of that of the completely silylated compound and that of tributanoyl glycerol. It is obvious that one equivalent of base per acyl group is not enough to give complete trienolate anion formation under the conditions used in the reaction. One possible explanation for this might be that some of the base is consumed before the addition of the triacyl glycerol, perhaps through a slow reaction of TMSCl with LDA [24]. Contrary to what we expected, the ^1H NMR spectrum also indicates that probably no products with one or two OTMS groups are formed. We assume that the reaction of the triacyl glycerol with the base and the following silylation are so fast that all available acyl groups react immediately when they get in contact with the base.

The results from the reaction of tridodecanoyl glycerol with LDA and TMSCl are similar to those mentioned above. One exception is that small amounts of starting material remain (10 mol-%) even when two equivalents of base per acyl group are used.

It is also possible to add the cooled base to a mixture of the triacyl glycerol and TMSCl (method B). By using this method we would always have the triacyl glycerol in excess and thus a greater possibility to trap the mixed silylated products. Reactions of tributanoyl glycerol according to method B were performed using 1 and 0.3 equivalents of LDA per acyl group. The resulting ketene acetals were analyzed by ^1H NMR. As when method A was used we identified the tri-O-silylated product and the starting material. With method B mixed silyl ketene acetal-acyl glycerols are probably also formed, since

the glycerol part of the spectrum shows additional peaks. In agreement with this four different α -acyl triplets, methylene sextets and methyl triplets are observed. The only apparent difference between the reactions performed with 1 and 0.3 equivalents of base is the amount of starting material left.

By hydrolysis of the trimethylsilyl ketene acetals we found (GLC-MS) that only minor amounts of C-silylated product were obtained. According to Rathke [6], the amount of C-silylated product is increased by substitution on the alcohol part of the ester, while O-silylation is favoured by substitution on the α -carbon. In alkanolic esters, excluding acetates, the amount of C-silylated products is small (about 10 %).

To alkylate the trimethylsilyl ketene acetals we applied the method described by Reetz and his coworkers [9,10]. The products from above, dissolved in methylene chloride, were added to anhydrous zinc chloride. To this mixture we added *t*-butyl chloride or 1-adamantyl bromide and stirred the resulting mixture at room temperature. The crude products were analyzed by GLC and/or HPLC, and then purified and isolated (Scheme 1). The pure triacyl glycerols were identified by ^1H NMR (Table IV), chemical ionization MS [29,35] (Table V) and elemental analyses (Table VI). As starting material in the alkylations we used the trimethylsilyl ketene acetals of tributanoyl and tridodecanoyl glycerol, but since the analyses of long chain triacyl glycerols are difficult, we performed most of the alkylation experiments with the use of *t*-butyl chloride and the trimethylsilyl ketene acetal of tributanoyl glycerol. The results of the *t*-butylation of tributanoyl glycerol, under

various conditions are summarized in Table III. The yields of recovered triacyl glycerols and the distribution of the different products were determined by GLC against hexadecane as internal standard. The products are numbered as in Scheme 1. The alkylation was followed by GLC. We found that the reaction was almost complete after 15 min, and from 1 h on, the composition of the triacyl glycerol mixture did not change, at least not until 108 h. It is evident from Table III, experiments 5-10, that even if we have almost complete formation of the trimethylsilyl ketene acetal with three OTMS groups, the *t*-butylation does not give only the tris- α -*t*-butylbutanoyl glycerol **3**. On the contrary the dominant product is bis- α -*t*-butylbutanoyl-butanoyl glycerol **2**, which is formed in about 50 % yield. The yield of compound **3** is not enhanced when the amount of *t*-butyl chloride is increased (entry 10). A tendency towards less alkylation is observed when the amount of zinc chloride is reduced (entry 9), and without catalyst no alkylated products are formed. The ^1H NMR spectra of the ketene acetals showed that starting material remained after reaction of the triacyl glycerol with only one equivalent of LDA per acyl group. This is in agreement with the results obtained after alkylation of these ketene acetals with *t*-butyl chloride (entries 1-3, 13). In experiments 1-3 we can see that the distributions of the *t*-butyl glycerols differ slightly from the distributions obtained in experiments 5 to 8.

The silyl ketene acetals prepared by method B were also alkylated (entries 4, 13). The recovery of triacyl glycerols was in these cases smaller than when the ketene acetals were

prepared by method A. In Addition only minor amounts of starting material were found in experiment 4. This suggests that the additional acyl groups found in the ^1H NMR of the ketene acetal might be a part of a mixed ketene acetal-acyl glycerol. Thus, in summary, the highest yields of α -t-butylated tributanoyl glycerols are obtained when the ketene acetal is prepared by the addition of the triglyceride to a cooled solution of two equivalents of LDA per acyl group and TMSCl . The ketene acetal formed is reacted with t-butyl chloride (one equiv./acyl group) in methylene chloride. The reaction is performed at room temperature with zinc chloride as catalyst. The reaction is complete after 1 h, but prolonged stirring has no negative effect. In this way, a mixture of α -t-butylated tributanols is formed. Under these conditions, we have not been able to prepare the trimethylsilyl ketene acetals selectively, and as a consequence we have not been able to alter the distribution of the alkylated tributanoyl glycerols to any great extent. But we obtain reproducible results when we perform the reaction under identical conditions. By repeated flash chromatography we have isolated small amounts of compounds 1, 2 and 3. The compounds were characterized by ^1H NMR (Table IV), chemical ionization MS (Table V), and elemental analyses (Table VI). The reaction conditions described above were also used to alkylate tributanoyl glycerol with 1-adamantyl bromide and tridodecanoyl glycerol with t-butyl chloride and 1-adamantyl bromide. The only difference was that the reaction time was at least 2 hours. The results of these reactions were more

complicated. All of the crude products contained (GLC, HPLC), in addition to the starting material, at least five triglycerides (Table VI). The total yields of these triacyl glycerols were determined by isolation of a triglyceride fraction by flash chromatography. The yields were determined in comparison to the theoretical yield of the corresponding trialkylated triacyl glycerol, and were found to be between 40 and 80 %. After laborious HPLC separations we managed to isolate the pure triacyl glycerols and identify them by ^1H NMR (Table IV) and chemical ionization MS (Table V). All of the isolated triglycerides are included in Scheme 1. Compounds 1-3 are formed in the reaction of tributanoyl glycerol with t-butyl chloride, compounds 4-8 are formed in the reaction of tributanoyl glycerol with 1-adamantyl bromide, compounds 9-14 are formed in the reaction of tridodecanoyl glycerol with t-butyl chloride and finally compounds 15-19 are formed in the reaction of tridodecanoyl glycerol with 1-adamantyl bromide. We have only determined the kinds and numbers of substituents that are incorporated in the triacyl glycerols, and not in which of the acyl groups (1, 2 or 3) they are situated. This means that the pure triacyl glycerol may contain many different isomers. Furthermore, we create new asymmetric centers when we prepare the α -alkylated products. Several diastereomers can thus be obtained. This is shown in the ^1H NMR spectra of the compounds (Table IV), where the glycerol part of the spectra in most cases is very complicated.

In Table V the dominant mass fragments obtained by chemical ionization mass spectrometry (NH_3) of the isolated compounds

are shown. All of the compounds except **19** give a molecular ion + NH_4 . In most cases this is the most abundant ion. Compound **19** has a molecular weight that is too high to be analyzed by the Finnigan instrument.

The distribution of the alkylated triacyl glycerols in the crude products were calculated from GLC or HPLC. The results are collected in Table VI. The GLC yields of compounds **1-3** were determined with hexadecane as internal standard. The amounts of compounds **4-8** were determined by the addition of known amounts of the pure triacyl glycerols. The HPLC distributions of compounds **9-14** and **15-19** were estimated by measuring the areas of the peaks. Poor separation of some of the triacyl glycerols makes the figures approximate.

One remarkable result in these alkylations is the formation of compounds containing α -trimethylsilyl groups. As mentioned above, the hydrolysis of the ketene acetals give only minor amounts of C-silylated triacyl glycerols (10 % at most). The α -trimethylsilyl groups are thus not introduced in the molecules by C-alkylation of the enolate anions. Instead, it seems reasonable to believe that the α -TMS derivatives are formed during the alkylation. To check this we treated the trimethylsilyl ketene acetal of tributanoyl glycerol with zinc chloride in the absence of alkylating agent. We followed the reaction on GLC and found that new compounds were beginning to form already after about 15 minutes, and from two hours on the composition of the mixture did not change. GLC-MS (CI) analyses showed that the compounds formed were triacyl glycerols containing one **20**, two **21** and three **22** α -trimethylsilyl groups (Scheme 2).

The di- and tri-substituted derivatives were formed in about equal amounts, 40 % each, according to GLC with hexadecane as internal standard. The remaining 20 % was divided between the starting material and the mono-substituted derivative. Desilylation of the crude product with potassium fluoride in DMSO [30] regenerated the starting material (Scheme 2). About 75 % of tributanol was recovered according to GLC. Similar results were obtained when the trimethylsilyl ketene acetal of tridodecanoyl glycerol was treated with zinc chloride in the absence of alkylating agent. HPLC analysis after two hours showed that most of the starting material was consumed. Three new products were formed, in yields of about 15 %, 34 % and 43 %. Desilylation of the crude product regenerated the tridodecanoyl glycerol. Probably we have a competition between the alkylation and the rearrangement in some cases. We have however not found that any α -trimethylsilylbutanoyl glycerols are formed in the *t*-butylation of the trimethylsilyl ketene acetal of tributanol glycerol. Unfortunately the α -trimethylsilyl butanoyl glycerols and the α -*t*-butylbutanoyl glycerols have the same retention times on GLC. But desilylation with potassium fluoride does not alter the product distribution in the *t*-butylated tributanol glycerol reaction mixtures. This means that all of the triacyl glycerols obtained are α -*t*-butylated and not α -silylated. The reaction of tributanol glycerol with *t*-butyl chloride is apparently more rapid than the rearrangement. The alkylation is almost complete after 15 minutes, while the rearrangement needs two hours to be almost complete. In the reactions of 1-adamantyl bromide with both the silyl ketene

acetal of tributanoyl glycerol and of tridodecanoyl glycerol we have found rearrangement products. We have also observed that the reaction with 1-adamantyl bromide required at least two hours to go to completion. In these cases the alkylation seems to be of comparable rate to the rearrangement. This is probably also true in the t-butylation of the ketene acetal of tridodecanoyl glycerol.

Rearrangements of trimethylsilyl ketene acetals by Lewis acids have been reported in the literature. Reetz and coworkers [9] have found that trimethylsilyl ketene acetals of acetates are impossible to alkylate with t-alkyl halides in the presence of zinc chloride due to such rearrangement to α -trimethylsilyl esters. No rearrangement of higher analogues were reported [9]. Lutsenko and his coworkers [25] have reported that the triethylsilyl ketene acetal of methyl acetate rearranges to methyl α -triethylsilyl acetate in the presence of mercuric iodide. In our case it is reasonable that steric factors might favour the intramolecular rearrangement compared to alkylation with sterically demanding halides.

The formation of the mixed α -trimethylsilyl- and α -t-alkyl glycerols is not a very serious problem in the preparation of the alkylated triacyl glycerols, since the α -TMS groups are easily removed by reaction with potassium fluoride (Scheme 3). The rearrangement itself might be a useful reaction, since the α -trimethylsilyl esters can be reacted further [31-33].

This investigation shows that it is possible to introduce sterically hindered groups into triacyl glycerols via the trimethylsilyl ketene acetals. Mixtures of compounds are always formed, but the triacyl glycerol fraction can easily be isolated

by chromatography. The individual triacyl glycerols can be isolated in pure forms, but for the time being only in small amounts. The stepwise syntheses of the corresponding triacyl glycerols from the branched fatty acids should be less advantageous, since the acids are sterically hindered.

Experimental

^1H NMR spectra were recorded on a Varian XL 300 NMR spectrometer. Chemical ionization mass spectra were obtained using a Finnigan 4021 mass spectrometer with ammonia as reagent gas [29,35]. Gas chromatographic analyses were performed on a Varian 1400 gas chromatograph equipped with a flame ionization detector. The column used was a 0.5 m glass column packed with 1.5 % of OV 1 on Gaschrom Q. HPLC analyses were carried out on the following equipment: LDC Constametric III pump; Rheodyne loop injector; Shimadzu UV spectrophotometric detector SPD-2AS operating at 215 nm. The column used was a 250 $\times$ 4.6 mm column packed with LiChrosphere C18 5 μ particles (Merck). For semi-preparative purposes, a 500 $\times$ 10 mm column packed with Polygosil C18 5 μ particles (Skandinaviska GeneTec AB) was used. As eluent we used different mixtures of methanol-diethyl ether.

Elemental analyses were made by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

Tetrahydrofuran was dried by refluxing over sodium followed by distillation under nitrogen. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves. Methylene chloride was refluxed over phosphorus pentoxide, distilled and filtered through a column of basic aluminium oxide (Merck). Trimethylsilyl chloride and t-butyl chloride (Merck) were distilled before use. 1-Adamantyl bromide and tributanoyl glycerol were purchased from Fluka and were used without purification. Tridodecanoyl glycerol was prepared by a standard procedure [26] from dodecanoyl chloride and glycerol. Anhydrous zinc chloride was prepared according to Pray [27].

Preparation of trimethylsilyl ketene acetals [7,8] from triacyl glycerols

A. With the addition of tributanoyl glycerol or tridodecanoyl glycerol to lithium diisopropylamide and trimethylsilyl chloride.
The reaction was carried out under nitrogen in dry glass equipment using the septum technique.

To a solution of 1.0 ml (7.2 mmol, 2.4 equiv./acyl group) of diisopropylamine in 8 ml of dry THF, 4.5 ml (6.7 mmol, 2.2 equiv./acyl group) of 1.48 M butyllithium in hexane was added at 0°C. The solution was stirred at 0°C for 15 min and was then cooled to -70°C. At that temperature a solution of 8.0 ml (60 mmol) of TMSCl in 12 ml of THF kept at -70°C was added via a cooled needle. The temperature was at no time allowed to rise above -65°C. When all of the TMSCl had been added, 1.0 mmol of triacyl glycerol in 8 ml of THF was added dropwise in such way that the temperature was -70° to -65°C. When the addition was complete, the clear solution was stirred at -70°C for another 15 min. The cooling bath was removed and the solution was allowed to reach room temperature. The solvent and the excess of TMSCl were then evaporated under nitrogen to avoid moisture and air. The residue was dissolved in 1 ml of methylene chloride and the salts were removed by filtration under nitrogen. The filtrate was used directly in the alkylation reactions described below.

In addition the reactions with 0.3, 1 and 10 equiv. of LDA per acyl group were carried out on tributanoyl glycerol.

Tridodecanoyl glycerol was reacted with 1 equiv. of LDA per acyl group.

For the use in ^1H NMR analyses the residue after evaporation above was dissolved in anhydrous CDCl_3 and filtered into a NMR tube under nitrogen. ^1H NMR shifts and coupling constants for the reaction products obtained are shown in Tables I and II, together with data for the starting triacyl glycerols.

B. With the addition of lithium diisopropylamide to a mixture of tributanoyl glycerol and trimethylsilyl chloride.

Lithium diisopropylamide was prepared as before from 0.5 ml (3.6 mmol, 1.2 equiv./acyl group) of diisopropylamine and 2.2 ml (3.3 mmol, 1.1 equiv./acyl group) of 1.48 M butyllithium in hexane. The solution of LDA in 4 ml of THF was cooled to -70°C . This solution was added dropwise through a cooled needle to a mixture of 0.30 g (0.29 ml, 10 mmol) of tributanoyl glycerol and 4.0 ml (30 mmol) of trimethylsilyl chloride in 14 ml of THF at -70°C . The temperature was not allowed to rise above -65°C during the reaction. When all of the LDA had been added, the mixture was stirred for another 15 min at -70°C and was then allowed to reach room temperature. The silyl ketene acetal was evaporated, dissolved in CH_2Cl_2 or CDCl_3 and filtered as above. The filtrate was used in further reactions or analysed by ^1H NMR.

In the same way tributanoyl glycerol was treated with 0.3 equiv. of LDA per acyl group.

The ^1H NMR results are summarized in Table I.

Reaction of the trimethylsilyl ketene acetals with
 τ -alkyl halides [9]

General description

The reaction was carried out in dry glass equipment under nitrogen.

The solution of the silyl ketene acetal from above, about 1 mmol in 1-2 ml of CH_2Cl_2 , was added to 0.20 g (1.5 mmol, 0.5 equiv./acyl group) of anhydrous zinc chloride [27]. To this mixture, 3 mmol of the alkylating agent, dissolved in 1 ml of CH_2Cl_2 if necessary, was added immediately with stirring. After 1-18 h of stirring at room temperature, water and methylene chloride were added. The organic layer was separated and the aqueous phase was extracted with methylene chloride. The combined organic layers were washed with saturated NaHCO_3 solution, water and saturated NaCl solution. After drying with MgSO_4 , the solvent was evaporated. The products were analysed by GLC and/or HPLC. Mixed triacylglycerol fractions were isolated by flash chromatography [28] on silica with hexane-diethyl ether 9:1 as eluent. Analytical samples of the different triacylglycerols formed were isolated and purified by repeated flash chromatography or repeated semipreparative HPLC. The purified α -substituted triacylglycerols were characterized by ^1H NMR and chemical ionization MS [29,35].

Trimethylsilyl ketene acetal of tributanoyl glycerol

a) with t-butyl chloride. Besides starting material, tributanoyl glycerols containing one **1**, two **2** and three **3** t-butyl groups were identified by GLC-MS (CI). The GLC distribution of these compounds was determined against hexadecane as internal standard. The results under different reaction conditions are summarized in Table III.

The t-butylated triglycerols obtained from 2.1 g (6.9 mmol) of tributanoin were isolated by flash chromatography as a triglyceride mixture in 53 % yield (1.7 g). (The theoretical yield of tris- α -t-butylbutanoyl glycerol **3** was 3.2 g.) The triacyl glycerols were separated by repeated flash chromatography. The yields of pure products were as follows: α -t-butylbutanoyl-dibutanoyl glycerol **1**: 0.31 g (13 %), $n_D^{25} = 1.4432$; bis- α -t-butylbutanoyl-butanoyl glycerol **2**: 0.61 g (21 %), $n_D^{25} = 1.4488$; tris- α -t-butylbutanoyl glycerol **3**: 0.14 g (4 %), $n_D^{25} = 1.4495$. Mixed triacyl glycerols (0.5 g) were also obtained. For ^1H NMR see Table IV, and for chemical ionization MS see Table V. Yields and elemental analyses are collected in Table VI.

b) with 1-adamantyl bromide. At least five products were formed according to GLC. Flash chromatography gave 0.7 g (39 %) of a triglyceride mixture. (The theoretical yield of tris- α -adamantylbutanoyl glycerol **8** was 1.8 g (2.5 mmol).) The triacyl glycerols in this mixture were isolated and purified in small quantities by repeated semipreparative HPLC. The products were analysed by ^1H NMR (Table IV) and chemical ionization MS (Table V): α -adamantylbutanoyl- α -trimethylsilylbutanoyl-butanoyl glycerol **4** (10 %);

α -adamantylbutanoyl-bis- α -trimethylsilylbutanoyl

glycerol **5** (7 %);

bis- α -adamantylbutanoyl-butanoyl glycerol **6** (12 %);

bis- α -adamantylbutanoyl- α -trimethylsilylbutanoyl

glycerol **7** (18 %); and

tris- α -adamantylbutanoyl glycerol **8** (23 %).

GLC yields in percent are calculated from the crude product by the addition of known amounts of the purified triglycerides. Yields and elemental analyses are summarized in Table VI.

Trimethylsilyl ketene acetal of tridodecanoyl glycerol

a) with t-butyl chloride. At least six products were formed according to HPLC. GLC gave very poor separation. Flash chromatography gave 0.4 g (50 %) of a triglyceride mixture. (The theoretical yield of tris- α -t-butyl-dodecanoyl glycerol **14** was 0.8 g, 1.0 mmol.) The triacyl glycerols in this mixture were isolated and purified by semipreparative HPLC. From ^1H NMR (Table IV) and chemical ionization MS (Table V) the compounds were identified as α -t-butyl-dodecanoyl-didodecanoyl glycerol **9** (22 %); didodecanoyl- α -trimethylsilyldodecanoyl glycerol **10** (14 %); α -t-butyl-dodecanoyl- α -trimethylsilyldodecanoyl-dodecanoyl glycerol **11** (24 %); bis- α -t-butyl-dodecanoyl-dodecanoyl glycerol **12** (25 %); bis- α -t-butyl-dodecanoyl- α -trimethylsilyldodecanoyl glycerol **13** (6 %); and tris- α -t-butyl-dodecanoyl glycerol **14** (7 %).

The product distribution in the crude product was calculated from HPLC. Yields and analyses are summarized in Table VI. Elemental analyses on the silylated triacyl glycerols were not carried out since insufficient amounts were isolated.

b) with 1-adamantyl bromide. At least five products were formed according to HPLC. Flash chromatography of the crude product gave 0.8 g (80 %) of a triglyceride mixture.

(Theoretical yield of tris- α -adamantyl-dodecanoyl glycerol **19** was 1.0 g, 1.0 mmol.) The five compounds in the mixture were isolated and purified by repeated semipreparative HPLC. From ^1H NMR (Table IV) and chemical ionization MS (Table V) the following structures of the compounds are proposed:

α -adamantyl-dodecanoyl- α -trimethylsilyl-dodecanoyl-dodecanoyl

glycerol **15** (4 %);

α -adamantyl-dodecanoyl-bis- α -trimethylsilyl-dodecanoyl

glycerol **16** (14 %);

bis- α -adamantyl-dodecanoyl-dodecanoyl glycerol **17** and

bis- α -adamantyl-dodecanoyl- α -trimethylsilyl-dodecanoyl

glycerol (**17** + **18**, 50 %); and

tris- α -adamantyl-dodecanoyl glycerol **19** (32 %).

The composition of the crude product in percent was calculated from HPLC, but since the resolution was not complete the figures are only approximate. Yields and analyses are collected in Table VI.

Rearrangement of the trimethylsilyl ketene acetal of
tributanoyl glycerol

The trimethylsilyl ketene acetal (1 mmol in 1-2 ml CH_2Cl_2) prepared as above was mixed with 0.20 g (1.5 mmol) of anhydrous zinc chloride. The mixture was stirred under nitrogen at room temperature for 18 h. The reaction mixture was then worked up as in the alkylations. GLC on the crude product showed that almost no starting material was left in the mixture, but instead three new products were formed. According to GLC-MS (chemical ionization) the products were α -trimethylsilylated tributanoyl glycerols (see Table V). The dominant ones were bis- α -trimethylsilylbutanoyl-butanoyl glycerol **21** and tris- α -trimethylsilylbutanoyl glycerol **22**, which were formed in equal amounts (0.16 mmol 40 % each). The remainder was α -trimethylsilylbutanoyl-di-butanoyl glycerol **20**, starting material and other unidentified products. The total yield of the silylated triacyl glycerols was about 40 % (0.4 mmol) determined by GLC with hexadecane as internal standard. The response factors were assumed to be the same as for tributanoyl glycerol.

Desilylation [30] of α -trimethylbutanoyl glycerols

To the crude product from above, containing about 0.4 mmol of triacyl glycerols corresponding to about 0.8 mmol of trimethylsilyl groups, 0.19 g (2 mmol) of $\text{KF} \cdot 2\text{H}_2\text{O}$ in 5 ml of DMSO was added. The mixture was stirred at room temperature over night and was then diluted with water and extracted with

ether. The combined ether layers were dried with MgSO_4 and analysed by GLC. All of the silylated triacyl glycerol had disappeared, and instead 0.3 mmol (75 %) of tributanoyl glycerol was obtained according to GLC.

Rearrangement of the trimethylsilyl ketene acetal of
tridodecanoyl glycerol

The ketene acetal (1 mmol) was treated with 0.20 g (1.5 mmol) of zinc chloride in CH_2Cl_2 . After two hours the reaction mixture was worked up. Most of the starting material was then consumed according to HPLC. Three new products were formed and their distribution was estimated to be 15 %, 34 % and 43 %. About 8 % of the starting material was also found.

Desilylation of the rearranged products with $\text{KF} \cdot 2\text{H}_2\text{O}$ as described before regenerated the starting material.

Desilylation of the crude product formed by alkylation of
tributanoyl glycerol with t-butyl chloride

The crude product (0.1 g including hexadecane) contained 12% of 1, 52 % of 2 and 34 % of 3, together with 2 % of tributanoyl glycerol. The mixture was treated with 0.1 g (1 mmol) of $\text{KF} \cdot 2\text{H}_2\text{O}$ in 2 ml of DMSO. GLC analysis of the desilylated product showed that the composition of the mixture had not changed. The distribu-

tion of the compounds was then: 15 % of **1**, 52 % of **2**, 31 % of **3** and 2 % of tributanoyl glycerol. The amounts were determined against hexadecane as internal standard. Almost no α -trimethylsilyl derivatives could thus have been present in the crude alkylated product.

Desilylation of the crude product formed by alkylation of tridodecanoyl glycerol with t-butyl chloride

The crude product (0.5 g) contained about 22 % of **9**, 14 % of **10**, 24 % of **11**, 25 % of **12**, 6 % of **13** and 7 % of **14**, together with 2 % of tridodecanoyl glycerol. This mixture was treated with 0.25 g (2.7 mmol) of $\text{KF} \cdot 2\text{H}_2\text{O}$ in 5 ml of DMSO. HPLC analysis of the desilylated product showed that the three peaks corresponding to the silyl-containing triacyl glycerols (**10**, **11** and **13**) had disappeared while the starting material together with the t-butyl substituted tridodecanoyl glycerols (**9**, **12**, **14**) remained. The distribution was now 41 % of **9**, 37 % of **12**, 9 % of **14** and 13 % of tridodecanoyl glycerol, see Scheme 3.

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Table I. ^1H NMR shifts for the reactions products formed in the reaction of tributanol glycerol with LDA and TMSCl

Ketene acetal formation		Chemical shifts in ppm					Coupling constants Hz	
1) Method	LDA equiv./acyl group	OTMS	-CH ₃	-CH ₂ -CH ₂ CO	CH ₂ CO	CH=	CH ₂ glycerol	CH glycerol
A	2	0.21(s)	0.890(t) 0.897(t)	-	1.965(p) 1.985(p)	3.64(t)	3.89(d)	4.37(p)
A	1	0.2(s)	0.884(t) 0.888(t) 0.931(t) 0.937(t)	1.63(sx) 1.64(sx)	1.961(p) 1.978(p)	3.639(t)	3.884(d) 4.140(dd) 4.292(dd)	4.364(p) 5.265(tt) J _{glycerol} =5 J _{alkyl} =7 J _{CH₂CH} =7
B	1 and 0.3	0.2(s)	0.898(t) 0.902(t) 0.946(t) 0.951(t)	1.648(sx) 1.655(sx) 1.659(sx) 1.665(sx)	1.98(p) 2.00(p)	3.655(t)	3.90(d) 4.16(dd) 4.31(dd) 3.8-4.0(m)	4.37(p) 5.22(tt)
Reference: tributanol glycerol								
			0.948(t) 0.955(t)	1.648(sx) 1.657(sx)	- 2.302(t) 2.310(t)	-	4.16(dd) 4.30(dd)	5.27(tt) J _{glycerol} =4,6,12

1) Method A: The triacyl glycerol is added to a cooled mixture of LDA and TMSCl.

Method B: LDA is added to a cooled mixture of the triacyl glycerol and TMSCl.

2) About 35 mol % unsubstituted acyl groups.

3) About 30 mol % unsubstituted acyl groups with 1 equiv. LDA and about 85 mol % unsubstituted acyl groups with 0.3 equiv. LDA.
t=triplet, d=doublet, dd=double doublet, sx=sextet, p=pentet, tt=triple triplet, m=multiplet, s=singlet.

Table II. ^1H NMR shifts of the reaction products formed in the reaction of tridodecanoyl glycerol with LDA and TMSCl

Ketene acetal formation		Chemical shifts in ppm									
1) Method	LDA equiv. / acyl group	OTMS	-CH ₃	-(CH ₂) ₈ -	CH ₂ -CH ₂ CO	CH ₂ CH=	CH ₂ CO	CH=	CH ₂ glycerol	CH glycerol	Coupling constants Hz
A	2	0.21(s)	0.87(t)	1.25(s)	-	1.9-2.0(m)	2)2.3(t)	3.64(t)	3.84(d) 4.10-4.33(dd)	4.37(p)	J _{a _{kyl}} =7 J _{CH₂CH} =7 J _{glycerol} =5
A	1	0.21(s)	0.87(t)	1.25(s)	1.6(m)	1.89-2.01(m)	3)2.307(t) 2.312(t)	3.64(t)	3.884(d) 4.14(dd) 4.29(dd)	4.367(p) 5.26(tt)	J _{a _{kyl}} =7 J _{CH₂CH} =7 J _{glycerol} =5,4,6,12
Reference: tridodecanoyl glycerol		-	0.87(t)	1.25(s)	1.6(m)	-	2.30(t) 2.31(t)	-	4.135(dd) 4.287(dd)	5.26(tt)	J _{a _{kyl}} =7 J _{glycerol} =4,6,12

1) Method A: The triacyl glycerol is added to a cooled mixture of LDA and TMSCl .

Method B: LDA is added to a cooled mixture of the triacyl glycerol and TMSCl .

2) About 10 mol % of unsubstituted acyl groups.

3) About 30 mol % of unsubstituted acyl groups.

Table III. GLC yields* and distribution of tributanol glycerols under various reaction conditions

Entry	Ketene acetal formation		Alkylation		Total GLC yield triacyl glycerol	GLC distribution tributyrin	1	2	3
	Method	LDA equiv./ acyl group	t-BuCl equiv./ acyl group	ZnCl ₂ equiv./ acyl group					
1	A	1	1	0.5	96	21	26	40	13
2	A	1	1	0.5	92	36	18	32	14
3	A	1	1	0.5	77	29	21	35	15
4	B	1	1	0.5	54	4	21	46	29
5	A	2	1	0.5	74	4	13	47	36
6	A	2	1	0.5	76	5	14	47	34
7	A	2	1	0.5	96	-	12	47	41
8	A	2	1	0.5	65	-	16	47	37
9	A	2	1	0.3	63	5	25	47	23
10	A	2	2	0.5	70	-	18	50	32
11	A	10	3	0.5	30	4	30	49	17
12	A	0.3	1	0.23	83	82	14	4	-
13	B	0.3	1	0.23	62	82	14	4	-

* determined against hexadecane as internal standard.

Table IV. ^1H NMR shifts of the substituted triacyl glycerols

Compound	TMS- -CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}- \\ \\ \text{CH}_3 \end{array}$	$(\text{CH}_2)_n$	CH_2CH	Adamantyl	CH-Si	CH-C	CH ₂ CO	CH ₂	CH
									glycero1	glycero1
1	-	0.877(t) 0.949(t)	0.962(s)	1.654(sx)	1.55-1.690(m)	-	-	2.104(dd) 2.294(t) 2.303(t)	4.163(m) 4.167(dd) 4.295(dd) 4.304(dd)	5.345(tt)
2	-	0.854(t) 0.860(t) 0.879(t) 0.949(t)	0.949(s) 0.963(s)	1.649(sx)	1.5-1-7(m)	-	-	2.094(dd) 2.06- 2.14(m)	4.07- 4.22(m) 4.22- 4.41(m)	5.22- 5.38(m)
3	-	0.853(t) 0.878(t)	0.948(s) 0.964(s)	-	1.478-1.690(m)	-	-	2.080(dd) 2.086(dd) 2.088(dd) 2.092(dd)	4.097- 4.267(m) 4.267- 4.415(m)	5.244- 5.334(m)
4	0.1(s)	0.833(t) 0.861(t) 0.879(t) 0.889(t) 0.947(t)	-	-	-	-	-	2.291(t)	4.091- 4.210(m) 4.240- 4.370(m)	5.267- 5.319(m)

Table IV Continued (1)

Compound	TMS-	-CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}- \\ \\ \text{CH}_3 \end{array}$	(CH ₂) _n	CH ₂ CH	Adamantyl	CH-Si	CH-C	CH ₂ CO	CH ₂ glycero	CH glycero
5	0.1(s)	0.835(t) 0.943(t) 0.955(t)	-			1.410- 1.965(m)			-	4.033- 4.420(m)	5.217- 5.308(m)
6	-	0.836(t) 0.841(t) 0.861(t) 0.945(t) 0.950(t)	-			1.407- 1.966(m)			2.289(t)	4.075- 4.231(m) 4.308- 4.400(m)	5.291- 5.377(m)
7	0.1(s)	0.860(t) 0.939(t) 0.946(t) 0.962(t)	-			1.410- 1.966(m)			-	4.025- 4.450(m)	5.241- 5.335(m)
8	-	0.840(t) 0.861(t) 0.811-0.891(m)				1.411- 1.968(m)			-	4.082- 4.229(m) 4.325- 4.453(m)	5.266- 5.348(m)

Table IV Continued (2)

Compound	TMS- -CH ₃	CH ₃ -C- CH ₃	(CH ₂) _n	CH ₂ CH	Adamantyl	CH-Si	CH-C	CH ₂ CO	CH ₂ glycerol	CH glycerol
9	-	0.942(s) 0.956(s)	1.262(s) 1.611(s)	1.4-1.6(m)	-	-	2.123- 2.188(m)	2.294(t) 2.302(t) 2.313(t)	4.106- 4.186(m) 4.254- 4.352(m)	5.054- 5.315(m)
10	0.1(s)	0.887(t)	-	1.5-1.62(m)	-	1.989(dd)	-	2.312(t) 2.314(t) 2.338(t)	4.06- 4.39(m)	5.22- 5.32(m)
11	0.1(s)	0.886(t)	0.946(s) 0.959(s)	1.258(s) 1.572(s)	-	1.984(dd) 1.948- 2.010(m)	2.124- 2.320(dd)	2.289(t) 2.296(t)	4.038- 4.393(m)	5.215- 5.323(m)
12	-	0.884(t)	0.943(s) 0.956(s)	1.2(s) 1.6(s)	-	-	2.113- 2.187(m)	2.281(t) 2.287(t) 2.291(t)	4.074- 4.199(m) 4.256- 4.390(m)	5.277- 5.355(m)
13	0.1(s)	0.888(t)	0.948(s) 0.964(s)	1.261(s) 1.6(s)	-	1.945- 1.995(m)	2.109- 2.177(m)	-	4.00- 4.42(m)	5.16- 5.34(m)
14	-	0.875(t)	0.934(s) 0.950(s)	1.248(s) 1.6(s)	-	-	2.139(m) 2.132(m)	-	4.074- 4.192(m) 4.278- 4.391(m)	5.228- 5.292(m)

Table IV Continued (3)

Compound	TMS-	-CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}- \\ \\ \text{CH}_3 \end{array}$	(CH ₂) _n	CH ₂ CH	Adamantyl	CH-Si	CH-C	CH ₂ CO	CH ₂	CH
15	0.1(s)	0.886(t)	-	1.259(s)	1.402-1.449(m)	1.571-2.04(m)			2.296(t)	4.018- 4.230(m) 4.233- 4.412(m)	5.174- 5.319(m)
16	0.1(s)	0.886(t)	-	1.258(s)	1.382-1.446(m)	1.563-2.04(m)			-	3.979- 4.232(m) 4.235- 4.396(m)	5.178- 5.310(m)
17	-	0.887(t)	-	1.261(s)	1.402-1.498(m)	1.501-2.025(m)			2.285(t) 2.289(t) 2.293(t)	4.080- 4.199(m) 4.299- 4.408(m)	5.227- 5.341
18	0.1(s)	0.886(t)	-	1.258(s)	1.367-1.504(m)	1.504-2.020(m)			-	4.057- 4.227(m) 4.263- 4.406(m)	5.197- 5.275(m)
19	-	0.886(t)	-	1.258(s)	1.351-1.475(m)	1.505-2.020(m)			-	4.051- 4.183(m) 4.333- 4.444(m)	5.232- 5.308(m)

Table V. Chemical ionization MS of the substituted triacyl glycerols

Compound	Molecular weight	Mass fragments m/e (rel. %)		
		M ⁺ +18	M ⁺ -RCOO	Others
1	358	376(100)	271(20)	215(30)
2	414	432(100)	327(10)	271(60)
3	470	488(100)	327(65)	
4	508	526(100)	349(50)	287(10) 152(40) 135(15)
5	580	598(100)	421(30)	359(10) 152(30) 135(20)
6	570	588(100)	483(5)	349(20) 152(50) 135(20)
7	642	660(100)	483(10)	421(5) 152(50) 135(25)
8	704	722(100)	483(30)	152(70) 135(30)
9	694	712(100)	495(5)	439(2)
10	710	728(100)	439(70)	
11	766	784(100)	495(50)	
12	750	768(100)	495(5)	
13	822	840(100)	-	
14	806	824(35)	551(3)	
		825(100)		
15	844	862(100)	573(10)	152(33)
16	916	934(40)	645(100)	583(2) 152(100) 135(40)
17	906	924(30)	707(5)	573(5) 152(100) 135(20)
		925(30)		
18	978	996(40)	707(25)	152(100) 135(25)
19*	1040	1058-	-	152(100) 135(40)
20	374	392(100)	287(2)	215(30)
21	446	464(100)	287(50)	
22	518	536(100)	359(65)	

* Compound 19 had too high molecular weight to be observed in the Finnigan mass spectrometer.

Reaction gas: NH₃.

Table VI. Elemental analyses, yields and distribution of
alkylated triacyl glycerols

Compound	Analyses (%)	Triglyceride fraction yield % ¹⁾	GLC or HPLC distribution %
1	Calcd C 63.66 H 9.56 Found C 62.95 H 9.43	53	12 (GLC) ²⁾
2	Calcd C 66.63 H 10.21 Found C 66.93 H 10.10		47
3	Calcd C 68.90 H 10.71 Found C 68.99 H 10.81		41
4	Calcd C 66.10 H 9.51 Found C 67.08 H 9.98	39	10 (GLC) ³⁾
5	Calcd C 64.09 H 9.72 Found C 65.01 H 9.86		7
6	Calcd C 73.65 H 9.54 Found C 73.72 H 9.56		12
7	Calcd C 70.98 H 9.72 Found C 72.37 H 9.84		18
8	Calcd C 76.66 H 9.72 Found C 74.97 H 9.62		23
9	Calcd C 74.30 H 11.89 Found C 74.21 H 11.88		22 (HPLC) ⁴⁾
10	Calcd ⁵⁾ Found	50	14
11	Calcd ⁵⁾ Found		24
12	Calcd C 75.15 H 12.08 Found C 75.15 H 12.12		25
13	Calcd ⁵⁾ Found		6
14	Calcd C 75.87 H 12.24 Found C 74.66 H 11.74		7

Table VI Continued (1)

Compound	Analyses (%)	Triglyceride fraction yield % ¹⁾	GLC or HPLC distribution %
15	Calcd 5) Found	80	4 (HPLC) ⁴⁾
16	Calcd C 71.99 H 11.42 Found C 73.02 H 11.38		14
17	Calcd C 78.09 H 11.33 Found C 77.52 H 11.30		50
18	Calcd C 76.02 H 11.32 Found C 76.52 H 11.53		
19	Found C 79.56 H 11.22 Calcd C 79.58 H 11.29		32

1) Isolated yield.

2) Determined against hexadecane.

3) Determined with addition of the pure compounds.

4) Calculated peak areas.

5) Insufficient amounts to be analyzed.

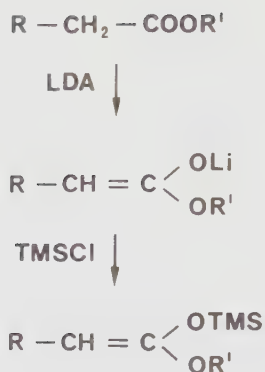


Figure 1. Formation of O-trimethylsilylketene acetals from ester enolate anions.

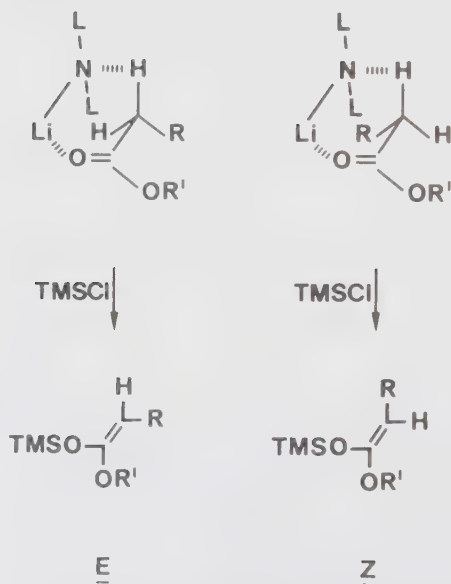
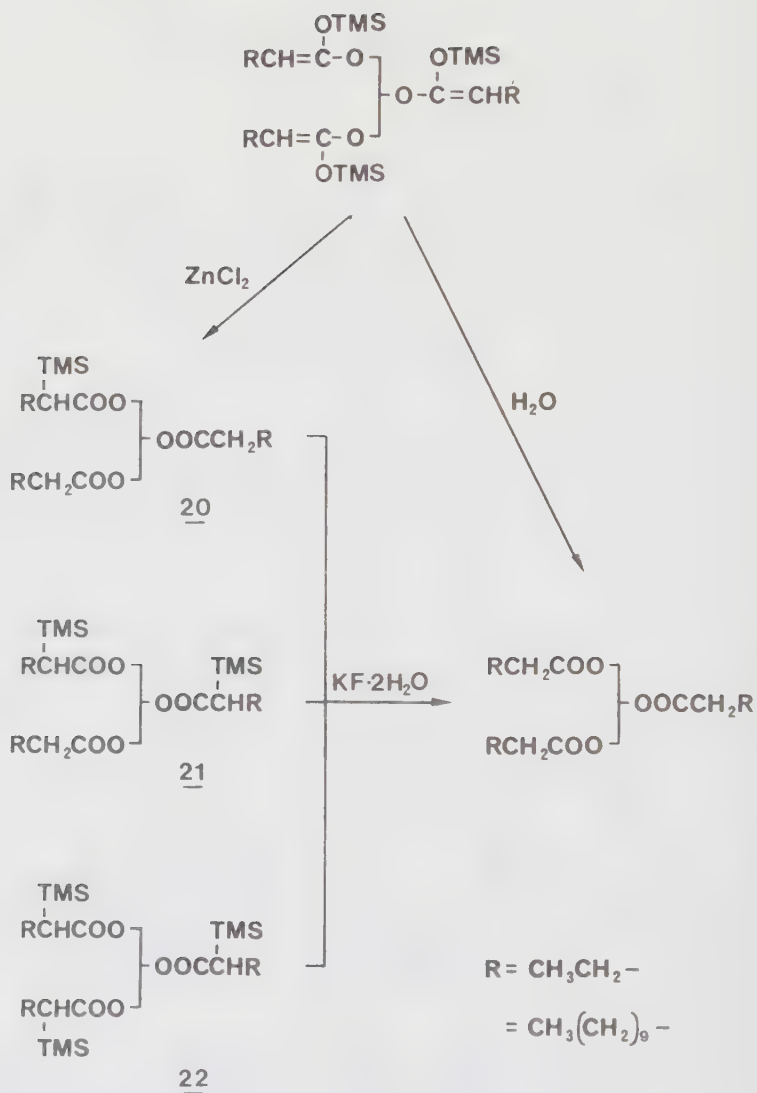
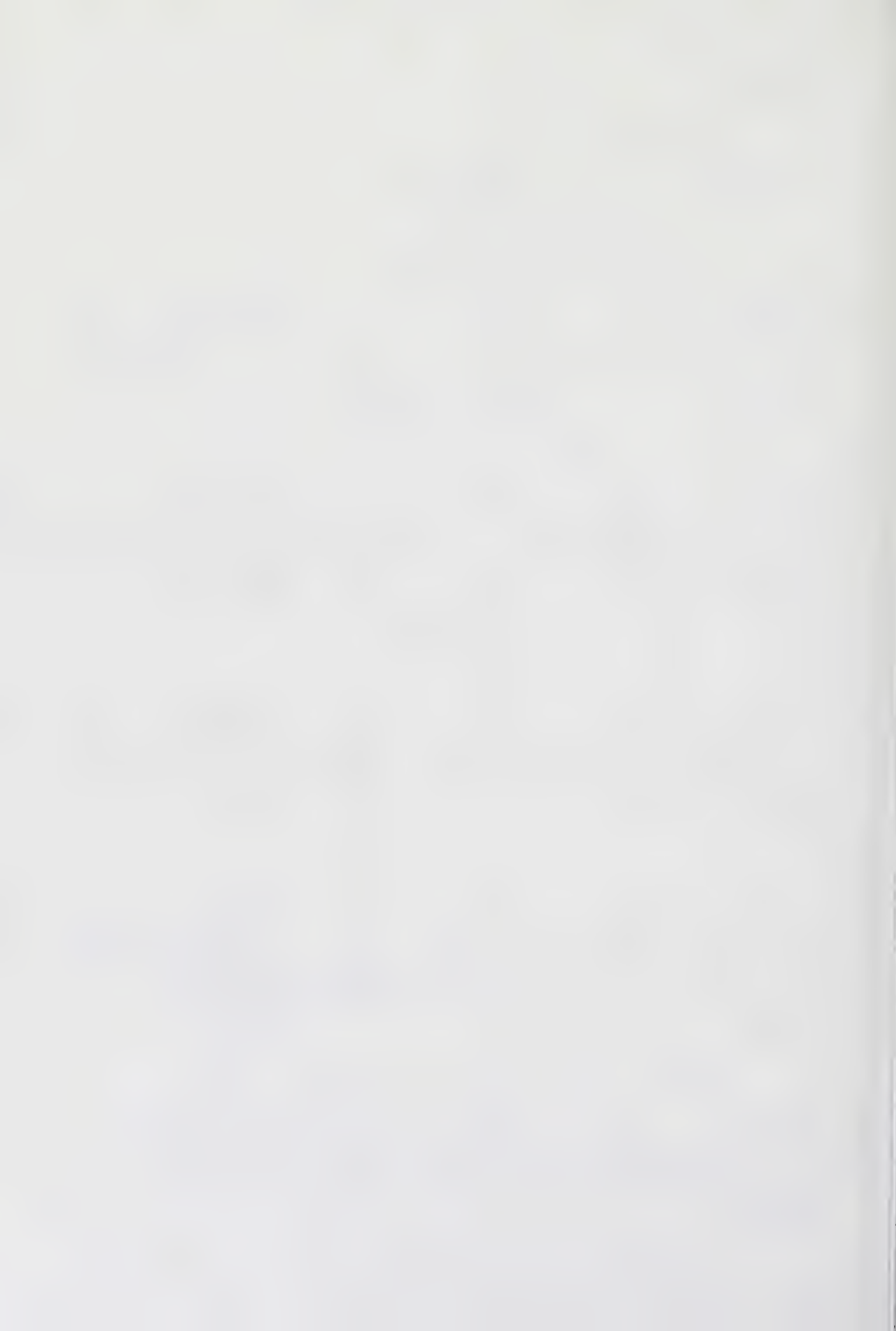


Figure 2. Possible transition states giving E and Z silyl ketene acetals.





Scheme 2. Formation of α -trimethylsilyl-substituted triacyl glycerols.



Simple Small Scale Preparations of Specific Triglycerides and Triglyceride Mixtures

By B. Herslöf, M. Herslöf and O. Podlaha*

Interesterification reactions between two fatty acid methyl esters and trilaurin are investigated. The reaction products are analyzed by HPLC and GC. Great correspondence is found between the calculated and experimental compositions. One of the components is collected from a semi-preparative HPLC-column. It shows a very high purity and can be used as a reference substance.

Introduction

The analysis of natural triglyceride mixtures is often very complex and requires several different operations. In such work model compounds are often needed. The synthetic pathways to triglycerides of defined structures are rather tedious and simpler procedures would be preferred. We would like to report on the investigation of such a procedure which we think can be useful in some cases.

Interesterification reactions are in general simple procedures which produce the expected mixture in almost quantitative yields. M. Naudet and P. Desnuelle¹ demonstrated this with triolein and tristearin. E. C. Nickell and O. S. Privett² used the reaction to prepare defined mixtures from other pairs of monoacid triglycerides. Numerous reports in the literature describe the interesterification of natural fats in technical and analytical amounts. However, for preparative purposes these types of reactions have been of limited value. E. Lutton and A. Fehl³ report the synthesis of monoacid triglycerides from sodium glyceroxide and fatty acid methyl esters, but di- and triacid triglycerides are generally prepared by stepwise synthetic routes.

The use of reversed phase HPLC in triglyceride separation has been described elsewhere⁴. The excellent separations which can be achieved encouraged us to use a semi-preparative HPLC-system to isolate specific triglyceride fractions, produced in interesterification reactions.

In a particular case we wanted to use a triglyceride containing heptadecenoic acid (17:1;H). This acid is rather expensive in highly purified form. To avoid too many chemical steps we carried out an interesterification reaction between the heptadecenoic acid methyl ester and trilaurin (LaLaLa). The reaction products were then separated on a reversed phase HPLC column and fractions were collected to isolate the different triglycerides.

The other example of this procedure is the interesterification of trilaurin and methyl palmitate (P) to pro-

Einfache Herstellung geringer Mengen von spezifischen Triglyceriden und Triglyceridgemischen

Die Umesterungsreaktionen zwischen zwei Fettsäuremethylestern und Trilaurin wurden untersucht. Die Reaktionsprodukte wurden durch HPLC und GC analysiert. Eine große Übereinstimmung zwischen den berechneten und experimentellen Werten konnte festgestellt werden. Eine der Komponenten wurde mit einer semi-präparativen HPLC-Kolonne isoliert. Sie hatte einen hohen Reinheitsgrad und kann als Referenzsubstanz benutzt werden.

duce a suitable mixture of triglycerides, which can be used as a standard for different purposes. We wanted to compare the distribution and quantitative representation of saturated triglycerides in GC and HPLC respectively.

Material

Analytical HPLC was carried out on the following equipment:

LDC Instrument Minipump 711 with damper; Rheodyne loop injector Model 7120; LCD Refracto-Monitor; 150 and 250 mm columns 4.6 mm I.D., packed with Nucleosil 5 μ C18 spherical particles (Macherey-Nagel).

Semi preparative HPLC was carried out with similar equipment:

Multiref RI-detector (Optilab AB); 250 mm column 10 mm I.D., packed with Polygosil 5 μ C18 irregular shaped particles (Macherey-Nagel).

All columns were slurry-packed with a Haskel pump at a pressure of 380 or 400 bar, according to the procedure described by P. Bristow⁵.

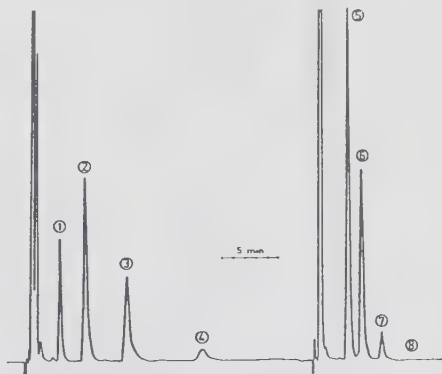


Fig. 1. HPLC of the reaction products from the interesterification experiments

Column: 150 mm; eluent: acetonitrile-acetone 1:1, 1.78 ml/min
Peaks: 1. LaLaLa, 2. LaLaP, 3. LaPP, 4. PPP, 5. LaLaLa, 6. LaLaH, 7. LaHH and 8. HHH (La = lauric, P = palmitic, H = heptadecenoic)

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¹ M. Naudet and P. Desnuelle, Bull. Soc. Chim. France 14, 323 (1947).

² E. C. Nickell and O. S. Privett, Separation Science 2, 307 (1967).

³ E. Lutton and A. Fehl, Lipids 5, 90 (1970).

⁴ B. Herslöf et al., J. Amer. Oil Chemists' Soc. 56, 864 (1979).

⁵ P. Bristow, Liquid Chromatography in Practice, HETP, England, 1976, p. 37.

Table 1

Distribution of the products from the interesterification reactions

A. Trilaurin/methyl heptadecenoate 2:1 (molar equivalents)

	Calculated statistical distribution		Experimental found values	
	[mol%]	[weight%]	GC*	HPLC**
LaLaLa	63.0	60.2	60.3	60.7
LaLaH	31.5	33.3	33.5	33.7
LaHH	5.3	6.2	5.9	5.2
HHH	0.3	0.4	0.3	0.4

B. Trilaurin/methyl palmitate 1:2 (molar equivalents)

	Calculated statistical distribution		Experimental found values	
	[mol%]	[weight%]	GC*	HPLC**
LaLaLa	21.6	19.5	21.8	20.6
LaLaP	43.2	42.5	43.0	44.0
LaPP	28.8	30.6	29.1	29.1
FPP	6.4	7.3	6.2	6.3

* OV 1 (3% on Gas-Chrom Q, 100–120 mesh); 50 cm;

Temperature program 225–350°C, 4%/min

** as Fig. 1

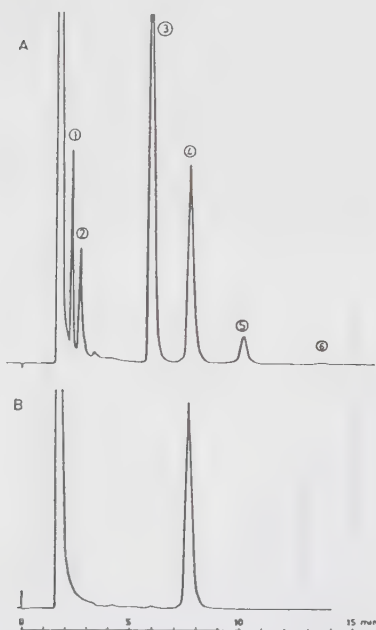


Fig. 2. HPLC of the reaction products from the interesterification reaction between trilaurin and methyl heptadecenoate. Column: 250 mm; eluent: acetonitrile-acetone 1:1, 1.78 ml/min

A represents the total sample (peaks: 1. methyl laurate, 2. methyl heptadecenoate, 3. LaLaLa, 4. LaLaH, 5. LaHH, 6. HHH); B is the chromatogram of the collected fraction (Fig. 3) which corresponds to peak 4 (LaLaH)

GC was carried out on Varian instruments (1400 and 2400) with flame ionization detectors. Glass columns (2 mm I.D.) were used.

Trilaurin and the methyl esters of palmitic and 10-heptadecenoic acid were purchased from Nu-Chek Prep. The purity of these compounds were better than 99%.

Experimental

The experimental conditions were similar to those reported by E. C. Nickell and O. S. Privett². The interesterification of trilaurin with the methyl ester of palmitic acid will be described in detail:

1.7 mmol trilaurin (1.08 g), 3.4 mmol methyl palmitate (0.91 g) and 10 mg sodium methoxide were mixed in a flask in a dry atmosphere of nitrogen. The mixture was stirred with a magnetic stirrer for 4 hours at 100°C. After cooling the reaction mixture was diluted with 25 ml methylene chloride and washed with three portions of distilled water. The organic phase was dried (MgSO₄) and directly used for chromatographic purposes.

Results

HPLC of the reaction products for the two examples studied are shown in Fig. 1. The calculated and experimentally found results are given in Table 1.

The reaction mixture from the trilaurin/methyl heptadecenoate interesterification (Fig. 2A) was submitted to the semi-preparative HPLC-column (Fig. 3). Appro-

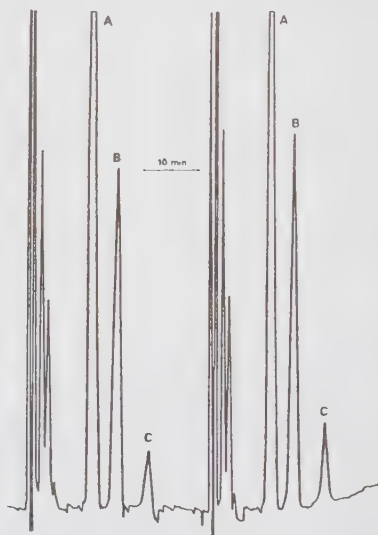


Fig. 3. Semi-preparative HPLC of the reaction mixture between trilaurin and methyl heptadecenoate. Column: 150 mm; eluent: methanol-acetone 3:2, 2.5 ml/min. Peaks: A. LaLaLa, B. LaLaH (collected), C. LaHH

ximately 20 mg total sample in 100 μ l chloroform was injected each time and ten injections gave about 50 mg pure substance from the collected peak (Fig. 2B). The

Table 2

Purity and composition of the collected HPLC-fraction

Carbon number distribution *	41	99.5 %
	La	H
Fatty acid composition, total (Mol%) **	66.1	33.9
Fatty acid composition, 2-position (Mol%) **	66.7	33.3

* GC as Table 1

** BDS (6% on Anadrom ABS, 100—110 mesh); 200 cm; temperature program 150—190°C, 2°/min

total as well as the 2-positional^a fatty acid composition was checked by GC (Table 2).

The expected statistical composition was confirmed by the experimental results and thus the fraction must consist of equimolar amounts of sn-LaLaH, sn-HLaLa (a racemic mixture) and LaHLa.

This well-defined mixture can be used as a reference compound in triglyceride analyses. It can serve different purposes. We intended to use it as an internal standard in silver ion chromatography. A specific amount of the mixture was added to a fat sample. The distribution of fatty acids in the 2-position of the monoenic

triglycerides was to be estimated and expressed as part of the distribution in the total sample. Silver ion TLC was performed and the mono-unsaturated triglycerides were scraped (including the added standard). The glycerides were extracted and transformed to the corresponding methyl esters. Routine GC-analysis gave the desired ratio.

The peak distributions in the reaction mixtures are almost identical for the two types of techniques used for separation. The results correlate very well with the expected statistical compositions (Table 1). This is an interesting observation since RI-detectors are one of few universal LC-detectors. Universal detectors are important in HPLC of lipids since such molecules rarely exhibit suitable UV-absorption. Our observations indicate that quantitative analyses of natural triglyceride mixtures could be performed with RI-detectors.

In conclusion we think that this method is simple, reliable and has many applications in analytical and small scale preparative glyceride chemistry.

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^a F. E. Luddy et al., J. Amer. Oil Chemists' Soc. 41, 693 [1964].





Polymorphism of Interesterified Triglycerides and Triglyceride Mixtures

By L. Hernqvist, B. Herslöf and M. Herslöf*

Complexes of well defined triglycerides have been produced by using interesterification. Simple triglycerides, i. e. triolein, trielaidin and tristearin, were used in the randomized interesterification reactions. The interesterified glycerides have been controlled analytically with high performance liquid chromatography. The polymorphic behaviour of the interesterified glycerides has been followed by recording of the diffraction pattern versus temperature. The result is compared with the polymorphic behaviour of the component triglycerides.

Introduction

The polymorphic behaviour of fats is important in many food systems, i. e. margarine and chocolate production. Information about the polymorphic forms and their transitions is therefore valuable.

Molecular arrangement in the α - and the β '-forms were recently proposed¹ which completes the earlier known structure of the β -form of simple triglycerides^{2,3}. Since the melt plays an important role when a fat crystallizes a structure of the melt was recently proposed⁴.

Most studies of the polymorphic behaviour have been done with simple triglycerides, well defined triglycerides or binary mixtures. When a fat crystallizes, usually a fraction of the fat dictates the overall crystallization. Since most technical fats consist of many different triglycerides, due to variation in chain length and saturation, the problem is often to understand which particular triglyceride fraction dominates the polymorphic behaviour.

To understand the polymorphic behaviour of a technical fat, both advanced analysis of the triglyceride composition and separate studies of each triglyceride fraction present is needed.

The present work deals with the possibility to study the polymorphic behaviour of complex glycerides formed by interesterification of simple triglycerides. The result is compared with the corresponding pure triglyceride systems.

The interesterification reaction of triglycerides has been reviewed in several articles⁵⁻⁷. Unless the reaction is directed, for instance by crystallization, the acyl radicals are distributed in the new glycerides in a statistically random manner^{5,6}. It is thus possible to obtain well defined systems of triglycerides where the amount of each new glyceride is determined by the composition of the starting triglycerides.

We have used the randomized interesterification reaction to prepare systems of triglycerides containing stearic, oleic and laidic acyl groups. The starting mixtures of triglycerides were chosen to produce glyceride systems that could serve as models for vegetable oils used in margarines.

The interesterified glycerides were investigated by means of high performance liquid chromatography, HPLC. For this specific purpose it was necessary to be able to quantify the amounts of different triglyceride species formed in the reaction in order to confirm that the distribution was equal to the one theoretically expected.

Polymorphie umgeesterter Triglyceride und Triglyceridmischungen

Mittels Umesterung wurden Komplexe wohl definierter Triglyceride erzeugt. Dabei wurden einfache Triglyceride wie z. B. Triolein, Trielaidin und Tristearin in der Random-Umesterung eingesetzt. Durch Hochdruckflüssigchromatographie wurden die umgeesterten Glyceride kontrolliert. Das polymorphe Verhalten der umgeesterten Glyceride wurde durch Aufnahme des Brechungsindex gegen die Temperatur verfolgt. Das Ergebnis wird mit dem polymorphen Verhalten der Triglyceridkomponenten verglichen.

HPLC of triglycerides has been reported in the literature since the mid-seventies. The earlier works utilized in most cases the RI detector^{8,9} but later also the UV detector was introduced in combination with solvent systems possible to use at short wavelengths¹⁰. For the present application both detection principles were used in combination with a solvent system especially developed to be able to elute the higher saturated triglycerides such as tristearin¹¹ which in many of the reported HPLC systems cause trouble to detect and quantify.

The composition of oils used when producing margarine dominates of C₁₈ hydrocarbon chains, stearin, olein and elaidin, i. e. a hydrogenated rapeseed oil with low content of erucic acid, LOBRA, consists of about 90% C₁₈ chains¹². This homogeneity in the chain length gives a very rapid transition from the β '-form to the β -form which develops large crystals and ends in a margarine with unacceptable texture (it produces a sandy feeling in the mouth, cf. ref. 13). Possibilities to hinder the β ' $\rightarrow$ β transition by using additives, like sorbitan stearate¹⁴ and diglycerides^{12,15} have been reported.

The possibility of using the variation in chain length to hinder the β ' $\rightarrow$ β transition is also shown in the present work.

Experimentals

Materials

The samples of 2-oleo-distearin (StOSt) and rac-1-oleo-distearin (OStSt) were prepared by standard methods. Triolein (OOO), trielaidin (EIEI) and tristearin (StStSt) were purchased from Sigma. Commercially available sodium methoxide was used as catalyst. In some reactions, lithium methoxide, prepared from methanol and butyllithium, was used.

Methods

Interesterification^{16,17}

0.68 mmol of the triglyceride AAA (see Table I) and 0.45 mmol of the triglyceride BBB were molten together in a reaction flask under a slow stream of nitrogen. About 5 mg of the catalyst (NaOMe or LiOMe) was added with stirring.

Table I

Starting triglycerides in the interesterification reaction

Starting triglycerides		Molar ratios AAA/BBB
AAA	BBB	
OOO	StStSt	3/2
EIEI	StStSt	3/2
OOO	EIEI	3/2

OOO = triolein
EIEI = trielaidin
StStSt = tristearin

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The reaction mixture was stirred at 100°C for 4 hours. After cooling, 25–30 ml of methylene chloride was added and the organic layer was washed with three portions of water. After drying with sodium sulphate, the solution was filtered through a short column of neutral alumina. The triglyceride fraction was evaporated to yield about 800 mg (65–88%) of TLC-pure product.

HPLC

HPLC was carried out on the following equipment: LDC Minipump 711 with pulse dampener; Rheodyne loop injector Model 7125; 250 mm column 4.6 mm ID; Nucleosil 5 µm C-18 stationary phase (Macherey-Nagel). The column was thermostated at 22°C. 200 µg of the triglyceride mixture was injected in 10 µl of hexane: isopropanol (1:1 v/v).

The solvent system was a ternary mixture consisting of acetonitrile, ethanol and hexane (40:35:25 v/v/v); all solvents were of spectroscopic grade.

The detection was performed with a Hewlett-Packard 1040 UV detector at 220 nm and an Altex Model 156 refractive index detector.

The chromatograms were recorded and integrated on a Shimadzu C-R2AX system.

X-Ray-Diffraction

A diffraction pattern *versus* temperature (DPT) camera¹⁸ was used. The X-ray films were examined with a photodensitometer. Immediately prior to the diffraction studies all samples were heated in the same way, i. e. heating for three minutes to a temperature of 30°C above the β-melting point, of the highest melting triglyceride fraction present, in order to destroy any "memory" of earlier crystals, and after that cooling to the temperature desired.

Results and Discussion

The different pairs of triglycerides used and their molar ratio are listed in Table 1. The molar ratio $3/2$ was chosen in order to give a solid-liquid ratio for the triolein-tristearin and the triolein-trielaidin systems similar to fats used in the margarine process.

The three investigated systems were each separated into the expected four peaks on the described HPLC system. The k' -values and the equivalent carbon numbers (ECN) are reported in Table 2. k' -Values are the normal way of expressing the retention behaviour of eluates in a HPLC system (cf. Table 2). The carbon number of a saturated triglyceride is defined as the number of carbon atoms in its fatty acids, i. e.

Table 2

ECN- and k' -values of the individual HPLC peaks from the three interesterification mixtures

Triglyceride type	Configuration	Experimental values	
Structure		ECN	k'
OOO	54:3 (c,c,c)	46.8	3.9
O ₂ El	54:3 (c,c,t)	47.3	4.1
OEl ₂	54:3 (c,t,t)	47.8	4.3
EIEIEI	54:3 (t,t,t)	48.2	4.5
O ₂ St	54:2 (c,c)	49.1	4.8
El ₂ St	54:2 (t,t)	50.0	5.3
OST ₂	54:1 (c)	51.4	6.2
ElSt ₂	54:1 (t)	51.9	6.5
StStSt	54:0	54	7.8

O = oleic

El = elaidic

St = stearic

ECN = equivalent carbon number

k' = capacity ratio; from $(t_r - t_0)/t_0$ where t_r is the retention time and t_0 the retention time of an unretained peak

54:3 (c,t,t) indicates one cis and two trans unsaturations

tristearin $3 \times 18 = 54$. The ECN-value of a triglyceride peak in HPLC is its experimentally found carbon number, calculated from a previous run of a set of saturated defined triglyceride species⁹. The chromatogram from one of the systems (trielaidin-tristearin) is shown in Fig. 1.

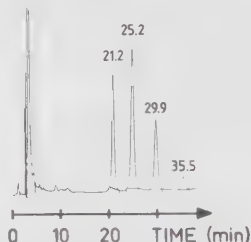


Fig. 1. HPLC of an interesterification system consisting of trielaidin and tristearin in the molar proportions 3:2; chromatographic conditions are as described in the text

The separated triglyceride types all have the same nominal carbon numbers (54) but different degree of unsaturation and configuration of the double bonds. This is the reason for using the ECN-values, which give the chromatographic relation to the saturated triglycerides.

The quantitative results are reported as area % in Table 3.

Table 3

Experimental results from HPLC determinations of interesterified systems of monoacid triglyceride pairs in the molar ratios 3:2

Triglyceride type	AAA	A ₂ B	AB ₂	BBB
Theoretical distribution (mol %)	21.6	43.2	28.8	6.4
Found distribution (area %)				
OOO/EIEIEI RI	21.9	44.7	27.6	5.8
UV	20.2	42.3	30.2	7.3
OOO/StStSt RI	23.2	43.8	26.7	6.3
UV	32.3	41.0	22.6	4.1
EIEIEI/StStSt RI	24.4	40.4	26.8	8.4
UV	28.1	43.0	24.1	4.8
OOO = triolein (always A)		RI = Refractive index detection		
EIEIEI = trielaidin		UV = UV detection		
StStSt = tristearin (always B)				

The general observation from these values is that the unsaturated triglycerides are overrepresented when the UV-detection is used, compared to the RI-detection. This is valid even if the wavelength is 220 nm. This is observed in the two systems containing both saturated and unsaturated triglycerides, i.e. triolein-tristearin and triolein-tristearin, but not observed in the system with only unsaturated compounds (triolein-trioleoin). In the last case similar representations for the UV- and RI-detectors are observed.

The general conclusion from the observed distributions is that the transesterification reaction has produced in each case a randomized mixture which corresponds well to the calculated composition. This has been demonstrated in the case of saturated triglycerides¹⁷ and the present investigation shows that there is no selectivity due to double bonds or their configurations.

In Fig. 2 the polymorphic transitions of the interesterified triolein-tristearin mixture is shown. The mixture is cooled

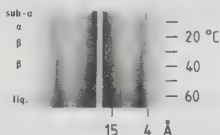


Fig. 2. DPT-diagram of the polymorphic transitions of an interesterified triolein-tristearin system, molar proportions 3 : 2; the mixture is cooled rapidly (80° C/min) down to 0° C and the DPT-diagram is then developed during slow heating (0.4° C/min)

rapidly (80° C/min) down to 0° C and the DPT-diagram is then developed during slow heating (0.4° C/min). Due to the rapid cooling the mixture crystallizes in the α -form and is then transformed to the sub- α -form on further cooling. The sub- α -form shows an extra line at 3.8 Å which indicates that the hydrocarbon chains are packed according to the orthorhombic subcell. When the temperature is raised the sub- $\alpha \rightarrow \alpha \rightarrow \beta \rightarrow$ transitions occur until the mixture finally melts at 56° C.

The different triglycerides present in the interesterified triolein-tristearin system and their theoretical molar proportions are: tristearin (StStSt) 6.4, 2-oleo-distearin (StOSt) 9.6, rac-1-oleo-distearin (OSSt) 19.2, rac-1-stearo-diolein (StOO) 28.8, 2-stearo-diolein (OSO) 14.4 and triolein (OOO) 21.6. The theoretical and the analysed composition is shown in Table 3. In this table the oleo-distearins and the stearo-dioleins, respectively, are not separated, i. e. $A_2B = 43.2$ is equal to $(StOO + OSO) = (28.8 + 14.4 = 43.2)$. Examination of the melting points of these triglycerides reveals that tristearin, 2-oleo-distearin and rac-1-oleo-distearin dominates the crystallization process when the mixture is cooled. These triglycerides are therefore examined, with DPT, both separately and blended, in order to understand the crystallization of the interesterified system.

The result of these DPT-studies is summarized in Fig. 3 (Polymorphic transitions when slowly heated [0.4° C/min] after rapid cooling [80° C/min]).

The rapid cooling of StOSt gives a sub- α -form that is transformed to α and β before melting occurs at 36.5° C (see Figs. 3 and 4). The long-spacing indicates a triple chain length order which is consistent with an earlier proposed structure²⁰ where the olein chain in the 2-position of the triglycerides is proposed to be segregated and packed in one layer. This triple chain length is persistent through all transitions. The

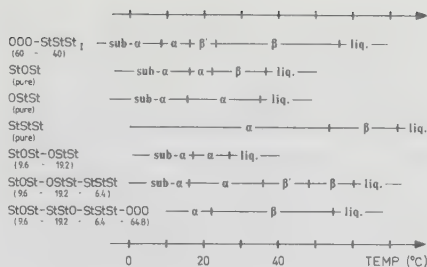


Fig. 3. Polymorphic transitions during slow heating (0.4° C/min) after rapid cooling (80° C/min) (based on DPT-diagrams as shown in Figs. 2 and 4); 1 = Interesterified mixture, molar proportions are given in brackets

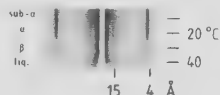


Fig. 4. DPT-diagram of the polymorphic transitions of 2-oleo-distearin; the sample is cooled rapidly (80° C/min) down to 0° C and the DPT-diagram is then developed during slow heating (0.4° C/min)

continuous shift of the inner long-spacing for the sub- α and α -forms reveals that the tilt of the hydrocarbon chains is continuously decreased – the d-value is shifted from about 38 Å at 0° C up to 46 Å when the temperature is 20° C. A similar behaviour has recently been shown for the α -form of 1-O-alkylglycerols (cf. Ref. 21).

The rapid cooling of OSSt gives a sub- α -form, which is transformed to the α -form at 15° C when the sample is slowly heated, and finally melts at 35° C. This triglyceride also shows triple chain length which perhaps is surprising since the unsaturated chains should be expected to be segregated in one layer if a triple chain length structure should exist. Hence the acyl chain in the 1-position in the triglyceride probably is oriented in the opposite direction to the others, contrary to the β -form of tridodecanoin, where the acyl chain in the 2-position is pointing in the opposite direction to the others⁸.

The StOSt-StStO mixture crystallizes in a sub- α -form when the sample is cooled rapidly. When the mixture is heated the sub- $\alpha \rightarrow \alpha \rightarrow$ liq. transition takes place. Both the sub- α -form and the α -form is packed in a double chain layer hence the unsaturated chains are not segregated. The relative low melting point, 27° C, is due to the fact that the packing is not optimal.

The StOSt-StStO-StStSt mixture also crystallizes in a sub- α -form when cooled rapidly. The mixture undergoes the transitions sub- $\alpha \rightarrow \alpha \rightarrow \beta \rightarrow$ before melting finally occurs at 60° C. A continuous shift of the long-spacing lines for the sub- α -form when the temperature increases indicates that the tilt of the chain decreases. This change, however, is somewhat smaller compared with the one obtained in the case of the pure 2-oleo-distearin sample (see Fig. 4). The melting point of 60° C indicates that co-crystallization occurs. The intensity of the long-spacing lines decreases continuously which must be due to variation in the homogeneity of the crystal packing.

Regions containing more tristearin melt later than regions dominated of oleo-distearin.

The final step in imitating the triolein-tristearin interester-

ified system was to add 64.8 molar percent of triolein. By assuming that StOO and OSStO do not influence the polymorphic behaviour this blend should be equal to the interesterified system.

This is, as can be seen in Fig. 3 not the case, the exclusion of both the sub- α and the β' -form indicates a difference. In the interesterified system in Fig. 2, the long-spacing for the sub- α and α -forms indicates the existence of a triple chain length order. However, when $\alpha \rightarrow \beta'$ transition occurs the triple chain order disappears and in the β' - and β -forms only the double chain order exists. The StOSt-StStO-StStSt-OOO mixture gives double chain order and not triple in the α -form. Since the melting points for StOO and OSStO fit with the disappearance of the triple chain length in the DPT-diagram of the interesterified mixture in Fig. 2 these differences must be due to the OOSSt and OSStO triglycerides present in the interesterified systems.

2-Decano-diolein was recently proposed to give a β -3 structure²² with the olein chains in the first and third positions in one layer.

The StOO and OSStO glycerides can either crystallize segregated from the rest of the triglycerides in a triple chain length arrangement or co-crystallize with the rest of the triglycerides present. The latter possibility should give a segregation of the oleic acyl chains in one layer and the stearic acyl chains packed together with stearic acyl chains. This would give a triple chain order with saturated chains in two layers and unsaturated chains in the third one. This proposition is based on the fact that the α -crystal forms are loosely packed, the mobility of the hydrocarbon chains is quite high, hence giving place for defects in the crystal packing.

When the temperature is raised the OSStO and StOO glycerides melt, this happens at the same time as the $\alpha \rightarrow \beta'$ transition occurs (the better chain packing in the β' -form excludes larger crystal deformations).

In order to study the influence of trans unsaturated fatty acids in a margarine oil blend, trielaidin was interesterified together with triolein and tristearin, respectively. The polymorphic behaviour of the triolein-trielaidin and the interesterified trielaidin-tristearin systems after rapid cooling (80° C/min) and then slowly heating (0.4° C/min), is shown in Fig. 5. In the same figure the polymorphic behaviour of a trielaidin-tristearin binary mixture, trielaidin and a binary mixture of the interesterified systems of triolein-tristearin and triolein-trielaidin with and without addition of 2-stearo-dipalmitin (PStP) is shown.

The polymorphic behaviour of the interesterified triolein-trielaidin system shows similarities with the interesterified triolein-tristearin system. The main difference is the absence of sub- α and α in the case of the triolein-trielaidin system. However, due to the lower melting point of elaidin all transitions are shifted to a lower temperature. As a consequence the sub- α and the α -form do not exist in the temperature region studied.

If the interesterified trielaidin-tristearin system, the trielaidin-tristearin binary mixture and trielaidin, see Fig. 5, are compared with tristearin in Fig. 3, the presence of triglycerides containing elaidin in a triglyceride mixture can be somewhat clarified.

Trielaidin seems to behave as tristearin, both crystallize in the α -form which is transformed to the β -form before final melting. It should be mentioned that even if the β' -form is not detected in these studies this does not exclude the possibility that the transitions should be $\alpha \rightarrow \beta' \rightarrow \beta$ -liq. The only differ-

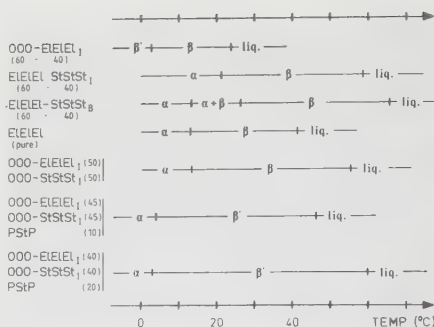


Fig. 5. Polymorphic transitions during slow heating (0.4° C/min) after rapid cooling (80° C/min) (based on DPT diagrams as shown in Figs. 2 and 4); I = Interesterified mixture, B = Binary mixture, molar proportions are given in brackets

ence between trielaidin and tristearin is a temperature shift.

The melting point of the β -form of the interesterified EIEI1-StStSt system is 58.5 which is more or less in between the melting points of the pure samples. The polymorphic behaviour is identical, i. e. $\alpha \rightarrow \beta$ -liq.

The binary mixture of trielaidin and tristearin (see Fig. 5) has a different behaviour. The presence of a two phase region, i. e. $\alpha + \beta$, indicates segregated crystallization. However, the final melting point of the β -form at 65.5° C is much lower than the melting point of pure tristearin (72° C). Hence, the triglycerides are not totally segregated.

If the two interesterified systems of triolein-trielaidin and triolein-tristearin are blended in the ratio 1:1 the obtained mixture is quite similar to a hydrogenated fat. Both what concerns the content of *trans*-unsaturated fatty acids and the solid-liquid ratio.

In a hydrogenated fat the position of the double bond varies, which excludes the possibility to arrange the double bonds exactly as in the case of i. e. 2-oleo-distearin²⁰. Nevertheless the interesterified mixture is quite close to a hydrogenated fat. The main difference being the uniform chain length which is eliminated by introducing 2-stearo-dipalmitin.

Due to the homogeneity of the chain length the blend of the interesterified systems is transformed to the β -form before melting. The interesterified mixtures containing 2-stearo-dipalmitin melts in the β' -form. The more PStP the higher the melting point. Examination of the short-spacing lines of the β' -form of the mixture containing 20% 2-stearo-dipalmitin (3.84 m; 4.06 w; 4.24 m; 4.37 w) reveals that these are identical with the β' -form of pure 2-stearo-dipalmitin (cf. Ref. 1). This domination on the crystallization is due to the high amount and the high melting point of the 2-stearo-dipalmitin.

It should be pointed out that interesterification is fruitful not only when studying the polymorphic behaviour but also as a possibility to avoid *trans*-unsaturated fatty acids. By total hydrogenation of a fat followed by interesterification with an actual oil, a fat with suitable crystallization properties could be produced. For nutritional reasons²³ the presence of *trans*-fatty acids in fat products can thus be avoided.

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**Polymorphism and Flow Behaviour of Some Low Melting
 α -Alkyl Branched Triacyl Glycerols**

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A b s t r a c t

The polymorphic behaviour of 1- α -n-butyl-dodecanoyl-2,3-didodecanoyl glycerol **1**, 1,2-bis- α -n-butyl-dodecanoyl-3-dodecanoyl glycerol **2**, tris- α -n-butyl-dodecanoyl glycerol **3** and tris- α -n-decyl-dodecanoyl glycerol **4** were studied using differential scanning calorimetry (DSC) and X-ray diffraction. The presence of one, two or three α -alkyl groups in the fatty acid of the triglyceride molecule shifts the liquid to solid transition to lower temperature. The compound containing one α -butyl group shows four different polymorphic forms, while the di- α -butyl substituted tridodecanoyl glycerol shows only one form.

The tris- α -n-butyl dodecanoyl glycerol probably could undergo a glass transition instead of a crystallization, as opposed to the tris- α -n-decyl dodecanoyl glycerol which shows several different polymorphic forms.

The transitions are confirmed by the viscosity measurements. The samples of **2** and **4** continue to show low viscosity at decreasing temperature until the crystallization takes place. The proposed glass transition of tris- α -n-butyl dodecanoyl glycerol is supported by the measurements of viscoelastic properties, i.e. the storage modulus G' and the loss modulus G'' .

I n t r o d u c t i o n

Vegetable oils play a small but important role as renewable resources in the chemical industry.¹ There is a growing interest in the development of new chemicals and modified vegetable oils with applications for instance as lubricants.

During the past few years we have studied synthetic modifications of lipid derivatives.²⁻⁵ We have prepared³ some α -n-alkyl branched triacyl glycerols (Fig. 1). These compounds are fully saturated and thus exhibit greater stability towards oxidation than the unsaturated triacyl glycerols. Furthermore we have noticed that these compounds have lower melting points than the corresponding straight chain analogues. Most remarkable was that tris- α -n-butyl dodecanoyl glycerol did not crystallize although it was cooled to -70°C . Since most unbranched saturated triacyl glycerols have a melting point well above 0°C the polymorphic and rheological behaviour of low melting α -alkyl branched triacyl glycerols seemed to be of further interest.

M a t e r i a l s a n d M e t h o d s

Syntheses

^1H NMR spectrum was recorded on a Varian XL 300 NMR spectrometer. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, West Germany.

The preparation of 1- α -n-butyl-dodecanoyl-2,3-didodecanoyl glycerol **1**, 1,2-bis- α -n-butyl-dodecanoyl-3-dodecanoyl glycerol **2** and tris- α -n-butyl-dodecanoyl glycerol **3** are previously described.^{2,3} Tris- α -n-decyl-dodecanoyl glycerol **4** was prepared according to standard procedures⁶ from α -n-decyl-dodecanoyl chloride and glycerol in 57 % yield.

^1H NMR (CDCl_3) δ = 0.88 ppm (t, $-\text{CH}_3$), δ = 1.25 ppm (s, $-\text{CH}_2-$), δ = 1.38-1.62 ppm (m, $-\text{CH}_2-\text{CH}<$), δ = 2.28-2.37 ppm (m, $>\text{CH}-\text{CO}$), δ = 4.06, 4.35 ppm (2st dd, $-\text{CH}_2-\text{O}-$), δ = 5.26 ppm (tt, $>\text{CH}-\text{O}-$), J = 4.15 Hz, 5.86 Hz, 11.96 Hz, (glycerol).

Elemental analysis: Calcd for $\text{C}_{69}\text{H}_{134}\text{O}_6$: C 78.20 %; H 12.77 %. Found: C 78.25 %; H 12.72 %.

The α -n-decyl-dodecanoyl chloride was prepared according to Ref. 2.

The purity of the triacyl glycerols were checked by GLC, HPLC and TLC before use. They showed one single peak and spot respectively.

Polymorphic studies

The DSC thermograms were collected using a Perkin Elmer DSC-2. The scanning rate was 2.5, 10 or $20^\circ\text{C}/\text{min}$. A diffraction pattern versus temperature (DPT) camera was used.⁷ The X-ray films were examined with a photodensitometer.

Rheological measurements

The rheological data were obtained on a Bohlin VOR Rheometer⁸ used in viscosity mode and in oscillation mode. The sample was contained between parallel plates with a gap size of typically 1 mm. The sample cell was positioned in a special low temperature environmental chamber cooled by a liquid nitrogen temperature controller (Fig. 2). In the parallel plate geometry the lower plate rotates (viscometry) or oscillates (oscillation) and the upper plate measures the resulting shear stress as a torque on the measuring shaft. To give high sensitivity this shaft is suspended by a frictionless air bearing. The torque sensitivity used was 10^{-2} Nm. The rheometer has a range of shear rates available from 10^{-3} to 10^{+3} s^{-1} . The small strain oscillation runs from strains of the order of 0.001 to 0.2 while the frequency range is 1 mHz to 20 Hz. The rheometer was routinely calibrated with a viscosity standard. The frequency of oscillation used in all oscillation tests was 1 Hz. The strain amplitude varied between 0.02 and 0.2. In the viscosimetry tests the shear rate was typically $50 s^{-1}$ but was lowered to $0.32 s^{-1}$ when the viscosity reading reached very high values in order to stay within the measuring range of the rheometer.

Results and Discussion

The DSC thermograms obtained when compounds **1**, **2** and **4** are cooled all show an exothermic transition. The temperatures of the phase transition were for 1- α -n-butyl-dodecanoyl-2,3-didodecanoyl glycerol **1** -20°C, for 1,2-bis- α -n-butyl-dodecanoyl-3-dodecanoyl glycerol **2** -28°C and for tris- α -n-decyl-dodecanoyl glycerol **4** -37°C. Due to experimental limitations we were not able to obtain any thermogram of the tris- α -n-butyl-dodecanoyl glycerol **3**.

When compounds **1** and **4** are heated they show both exothermic and endothermic transitions, compound **2** shows only one endothermic transition. The final melting point (heating speed 10°C/min) of **1** is +19°C, of **2** is -24°C and of **4** is +11°C.

To be able to determine if the compounds crystallize and show more than one polymorphic form, they were examined with X-ray diffraction. Compound **1** shows four different forms^{9,10} with the hydrocarbon chains arranged according to hexagonal, orthorhombic and triclinic subcells¹¹ respectively with increasing temperature. Compound **2** shows one form with the hydrocarbon chains arranged according to a hexagonal subcell. Finally compound **4** shows four different forms with the hydrocarbon chains arranged according to hexagonal, orthorhombic and triclinic subcells respectively. Since the hydrocarbon chains of the 2-alkyl branched triacyl glycerols are packed in the same way as ordinary straight chain analogues, we suggest that the same nomenclature¹² could be used. The different polymorphic forms of the α -n-alkyl-dodecanoyl glycerols can thus be named α , β_2' , β_1' and β .

Since single crystal examinations can hardly be done on these kinds of compounds, the exact arrangement of for example the glycerol part of the molecule can not be determined. However the long spacing data of the X-ray powder diffraction studies reveals that all polymorphic forms of the compounds studied seem to have tilted hydrocarbon chains towards the methyl end group plane, except the α -form of the tris- α -n-decyldodecanoyl glycerol.

The molecular arrangement of the β -form of trilaurin¹³ reveals that triacyl glycerols normally are packed head to head in a bilayer, the glycerol groups in the centre and the hydrocarbon chains pointing out in two directions. If the hydrocarbon chains are tilted, the distance between the glycerol parts in two different triacyl glycerol molecules can be increased, leaving room for the extra butyl chains, still having the hydrocarbon chains close-packed.¹⁴ In Figure 3, the main features of the molecular packing of the α -alkyl-branched triacyl glycerols are proposed.

Since the liquid to solid transition for 1- α -n-butyldodecanoyl-2,3-didodecanoyl glycerol and 1,2-bis- α -n-butyldodecanoyl-3-dodecanoyl glycerol takes place at -20°C and -28°C respectively, it is not surprising that tris- α -n-butyldodecanoyl glycerol is in the liquid state down to -70°C. The third butyl chain is obviously hard to arrange into a crystalline lattice. The 1,2-bis- α -n-butyldodecanoyl-3-dodecanoyl glycerol only crystallizes in one polymorphic form, the α -form. Since this form shows oscillating mobility of the hydrocarbon chains,⁹ which is

not the case for the β' and β forms, the α -form accepts more irregular molecules, for example branched molecules. The three butyl groups in the tris- α -n-butyl-dodecanoyl glycerol however, may give too much irregularity for close-packing even in the α -form. A glass transition instead of a true crystallization might occur when cooling this compound.

In order to get some information about the arrangement of the triglyceride molecules in the case of tris- α -n-butyl-dodecanoyl glycerol all compounds were studied using X-ray scattering technique. The dominating intensity in the long-spacing region has been interpreted as the bilayer thickness.^{15,16} The result is shown in Table I.

Since the bilayer thickness is constant from the melting point up to at least 50°C above the melting point¹⁶ all samples have been studied 50°C over the melting point.

All α -alkyl branched triacyl glycerols examined show shorter bilayer thickness compared with trilaurin. This indicates that the former compounds are somewhat looser arranged compared to the latter. Nevertheless the α -alkyl branched triacyl glycerols probably are arranged in a similar way as ordinary unbranched triglycerides.¹⁶ In agreement with the differences discussed above, the tris- α -n-butyl-dodecanoyl glycerol shows a much shorter bilayer thickness.

Due to the relatively high melting point (+19°C), the rheological properties of compound 1 were not studied. The steady shear rate viscosity (η) measurements of compounds 2, 3 and 4 are performed at a constant shear rate as a function

of temperature down to -71°C . The oscillatory viscoelastic properties are measured at a constant frequency at a small shear strain as a function of decreasing temperature. Oscillatory viscoelastic properties are for instance the storage modulus G' , a measure of the elastic component and the loss modulus G'' a measure of the viscous component of the sample. Related to G'' are the dynamic viscosity η' , which is also measured.

As evident from the DSC and X-ray studies discussed above compound **4** crystallizes when cooled. The result from the rheological study confirms this finding. Both **2** and **4** show low viscosity until they reach the crystallization area at about -30°C . In Figure 4 the viscosity (η) and the dynamic viscosity (η') of **4** as a function of temperature are shown. As can be seen the viscosity is low until the sample is cooled down to about -30°C where it crystallizes. It appears from the results that the crystallization is influenced by the difference in measuring technique used. In the measurement of the dynamic viscosity no orientation of the molecules is obtained because of the alternating small strains used. In the viscosity measurement the shear strain is large, indicating an orientation which favours crystallization and gives higher viscosity (dotted line in Figure 4). Neither **2** nor **4** showed any viscoelastic properties.

The behaviour of **3** was different. Instead of a crystallization we found evidence for a glass transition when the temperature was decreased. This is shown in Figure 5 where the storage modulus G' and the loss modulus G'' are plotted against the

temperature. The G' curve is slowly increasing with decreasing temperature from about -53°C down to -68°C . This indicates an increase in the elastic component of the sample and that a glass transition takes place rather than a crystallization. The G'' curve is also slowly increasing with decreasing temperature and reaches a maximum at about -68°C . At -71°C the end of the range of the rheometer was reached. To emphasize the different nature of the crystallization and glass transition in a viscosity versus temperature plot, **3** and **4** are compared on the same scale in Figure 6. In Figure 7 the dynamic viscosity (η') and the viscosity (η) are plotted against the temperature. As for compound **4**, the two curves differ depending on the measuring technique used. In this case, however, the effect is opposite. The transition appears to take place at higher temperature when the molecules are oriented by the flow field during the steady flow viscosity measurement.

One conclusion of this study is that tris- α -n-butyldecanoyl glycerol is a compound with unique physical properties. Further studies are needed to confirm the proposed glass transition. The very low temperature when the transition occurs together with the oxidation stability should make tris- α -n-butyldecanoyl glycerol interesting for technical use.

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A c k n o w l e d g e m e n t s

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Table I

Bilayer thickness of some α -alkyl branched triacyl glycerols

Compound	Temp. ($^{\circ}\text{C}$)	d($\text{\AA}$)
1	+70	18.9
2	+25	18.7
3	-20	16.5
4	+60	18.2
LaLaLa*	+95	20.0

*LaLaLa = Trilauroyl glycerol¹⁶

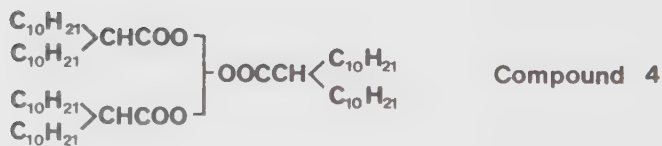
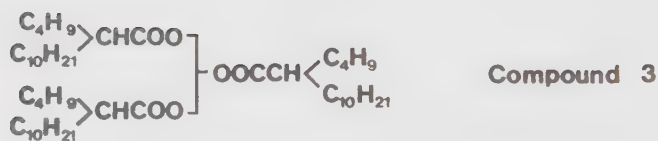
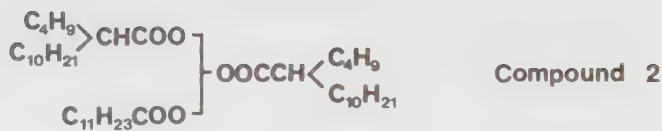
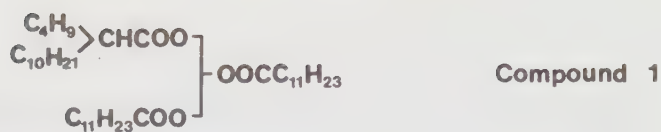


Figure 1. Studied α -alkyl branched triacyl glycerols.

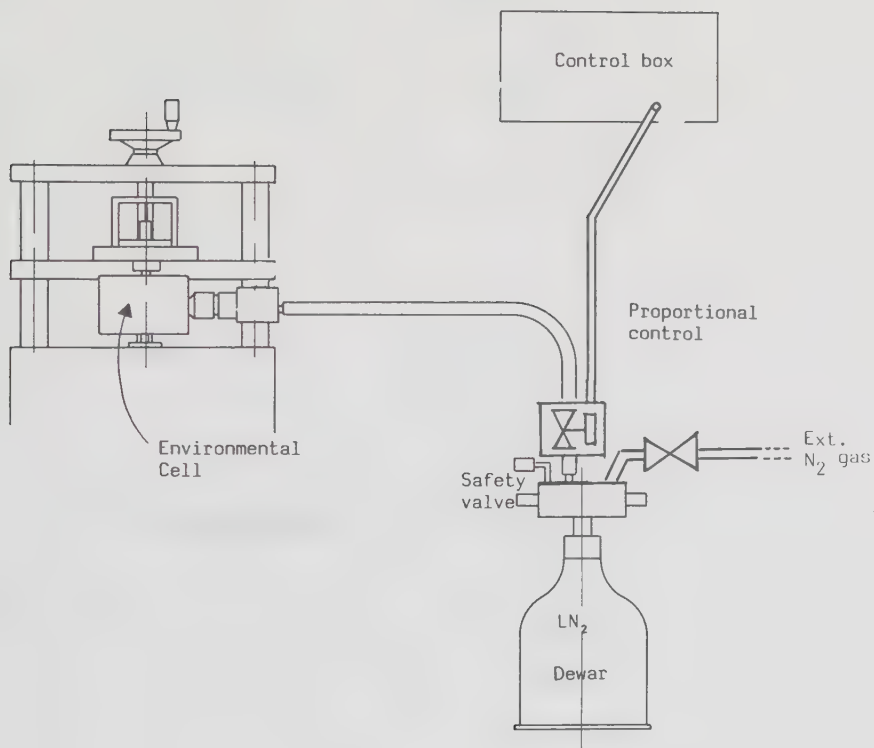
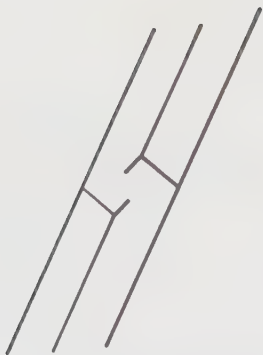
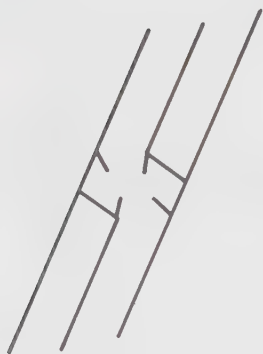


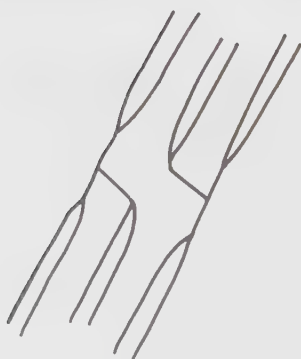
Figure 2. Low temperature device used in the viscosity measurements.



compound 1



compound 2



compound 4

Figure 3. Proposed molecular packing of α -alkyl branched triacyl glycerols.

Fig. 4
Compound 4

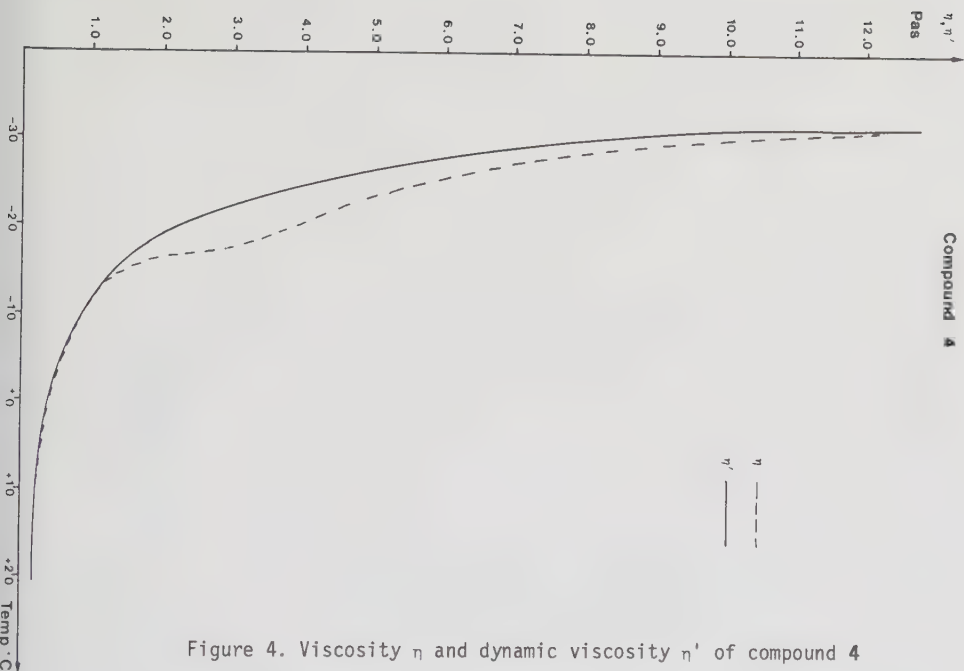


Figure 4. Viscosity η and dynamic viscosity η' of compound 4 as a function of temperature.

Fig. 5
Compound 3

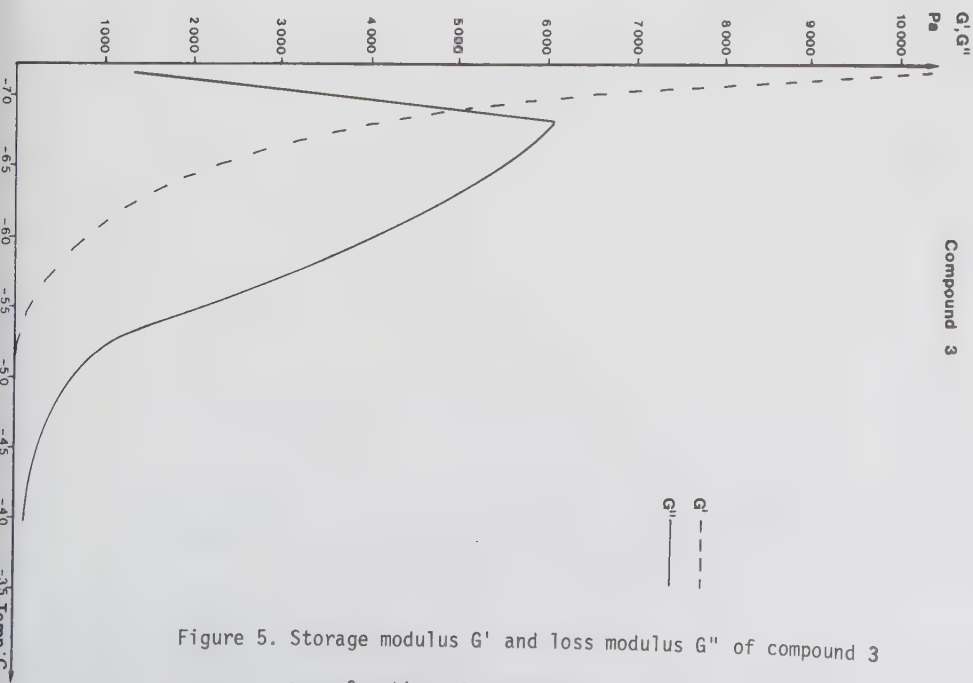


Figure 5. Storage modulus G' and loss modulus G'' of compound 3 as a function of temperature.

Fig. 6

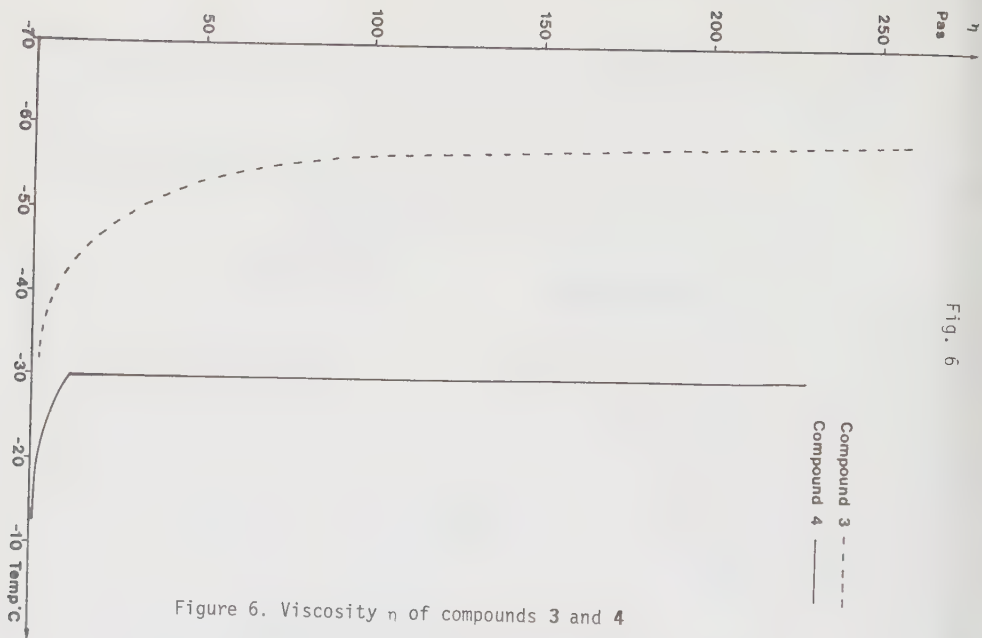


Figure 6. Viscosity η of compounds 3 and 4 as a function of temperature.

Fig. 7

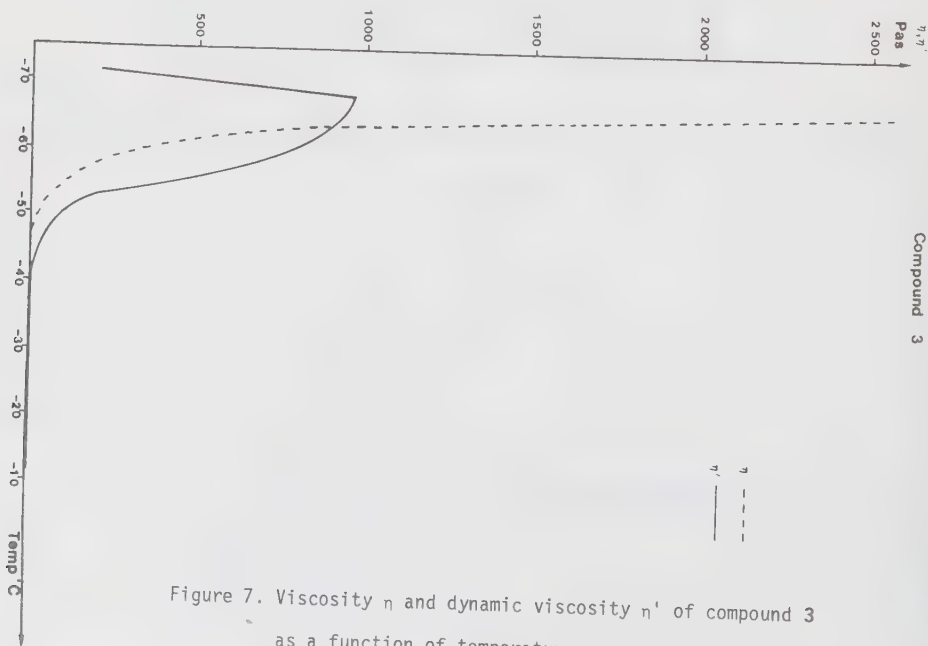


Figure 7. Viscosity η and dynamic viscosity η' of compound 3 as a function of temperature.

